

จริยธรรมในการวิจัยการดูแลสุขภาพ ในประเทศกำลังพัฒนา

คณะกรรมการชีวจริยธรรมนัฟฟิลด์
(Nuffield Council on Bioethics)



ชื่อหนังสือ : จริยธรรมในการวิจัยการดูแลสุขภาพในประเทศกำลังพัฒนา

The ethics of research related to healthcare in developing countries

ผู้แปล : นายแพทย์วิชัย โชควิวัฒน์
นางสาวนุสรา ไทยธวัช
นายธีรเดช อุทัยวิทยารัตน์

ISBN : 978-616-11-0106-0

ฝ่ายประสานงาน : นายแพทย์ปกรณ์ ศิริียง
นางปาริณา หุ่นจำลอง
นางวันเพ็ญ เย็นเพชร
นางสาวสุภาภรณ์ บุญปก
นางสาววาสนา ชาแสน
นางสาวสุธิดา แสนหล้า
นางพาฝัน ธนาศิริวัฒน์

พิมพ์ครั้งแรก : กันยายน 2552

จัดพิมพ์โดย

สถาบันพัฒนาการคุ้มครองการวิจัยในมนุษย์

อาคาร 8 ชั้น 7 อาคารกรมวิทยาศาสตร์การแพทย์ กระทรวงสาธารณสุข

ถ.ติวานนท์ อ.เมือง จ.นนทบุรี 11000

โทร. 0 2591 3517 , 0 2591 3541 โทรสาร 0 2591 4125

อนุญาตให้นำไปใช้เพื่อการอ้างอิงหรือเผยแพร่เพื่อประโยชน์ในทางวิชาการ หรือเพื่อส่งเสริม
การคุ้มครองการวิจัยในมนุษย์ และขอความร่วมมือในการอ้างอิงแหล่งที่มาด้วย

คำนำ

การพัฒนาปัญญาทางพุทธศาสนาประกอบด้วยแนวทางสำคัญสองแนวทาง ได้แก่ 1) หลักโยนิโสมนสิการ คือการพิจารณาไตร่ตรอง สำรวจตนเอง และ 2) หลักปรโตโฆสะ คือการศึกษาจากกัลยาณมิตร. การศึกษาทำความเข้าใจกับเรื่องจริยธรรม ซึ่งเป็นเรื่องทางนามธรรม โดยเฉพาะเรื่องจริยธรรมการวิจัย ซึ่งเป็นเรื่องค่อนข้างใหม่ในสังคมไทยจำเป็นต้องใช้หลักการทั้งสองข้อนี้เช่นเดียวกัน

เอกสารเรื่อง “จริยธรรมการวิจัยการดูแลสุขภาพในประเทศกำลังพัฒนา (The ethics of research related to healthcare in developing countries) ของคณะกรรมการชีวจริยธรรมนัฟฟิลด์ (Nuffield Council on Bioethics) เป็นเอกสารเกี่ยวกับจริยธรรมการวิจัยในมนุษย์ที่น่าสนใจ เพราะเป็นผลงานที่มุ่งเน้นการหาแนวทางดำเนินการที่เหมาะสมเมื่อต้องทำการศึกษาวิจัยในประเทศกำลังพัฒนาซึ่งมักมีบริบททางประเพณีวัฒนธรรมที่แตกต่างกัน โดยได้หยิบยกประเด็นสำคัญของจริยธรรมการวิจัย 4 ประเด็น คือ 1) การขอความยินยอม 2) มาตรฐานการดูแลรักษา 3) การทบทวนจริยธรรมการวิจัย และ 4) สิ่งที่ควรเกิดขึ้นหลังการวิจัยสิ้นสุดลง มาอภิปรายและเสนอทางออกที่น่าสนใจ การได้อ่านเอกสารนี้เสมือนการได้เสวนากับกัลยาณมิตร

สถาบันพัฒนาการคุ้มครองการวิจัยในมนุษย์ เห็นประโยชน์ของเอกสารฉบับนี้และเห็นสมควรที่ประชาคมวิจัยในมนุษย์ทุกภาคส่วน โดยเฉพาะผู้ที่ไม่ชัดเจนกับภาษาอังกฤษจะได้ศึกษาอย่างกว้างขวาง จึงได้มีการแปลและตีพิมพ์เผยแพร่ แม้เอกสารนี้จะตีพิมพ์ครั้งแรกหลายปีแล้ว แต่ก็ยังมีความทันสมัยและมีประโยชน์มาก หวังว่าเอกสารนี้จะก่อประโยชน์แก่แวดวงผู้เกี่ยวข้องในวงการศึกษาวิจัยในมนุษย์ตามสมควร สถาบันฯยินดีน้อมรับคำติชมด้วยมนสิการเสมอ และขอขอบคุณคณะกรรมการชีวจริยธรรมนัฟฟิลด์ มา ณ ที่นี้

สถาบันพัฒนาการคุ้มครองการวิจัยในมนุษย์

กันยายน 2552

จริยธรรมในการวิจัยการดูแลสุขภาพในประเทศกำลังพัฒนา

คณะกรรมการชีวจริยธรรมนัฟฟิลด์ (Nuffield Council on Bioethics)

จัดพิมพ์โดย :

Nuffield Council on Bioethics

28 Bedford Square

London WC1B 3JS

โทรศัพท์ 020 7681 9619

โทรสาร 020 7637 1712

อีเมลล์ : bioethics@nuffieldbioethics.org

เว็บไซต์ : <http://www.nuffieldbioethics.org>

เลขมาตรฐานสากลประจำหนังสือ (ISBN) 0 9522701 9 6

เมษายน 2002

ผู้ที่ต้องการหนังสือเล่มนี้ สามารถติดต่อไปยัง Nuffield Council หรือเข้าไปที่เว็บไซต์

เจ้าของลิขสิทธิ์ Nuffield Council on Bioethics 2002

สงวนลิขสิทธิ์ ห้ามพิมพ์ซ้ำ เก็บรักษา หรือแก้ไขดัดแปลงส่วนใดส่วนหนึ่งของหนังสือเล่มนี้ ไม่
ว่าในรูปแบบหรือด้วยวิธีการใด ก่อนที่จะได้รับอนุญาตจากเจ้าของลิขสิทธิ์ นอกเหนือจากการ
ปฏิบัติอย่างเป็นธรรม (fair dealing) เพื่อวัตถุประสงค์ในการศึกษา วิจัย วิพากษ์วิจารณ์ หรือ
เพื่อการทบทวน

พิมพ์โดย Latimer Trend Group

Estover Road

Plymouth PL6 7PY

ออกแบบปกโดย Geoffrey Wadsley

จริยธรรมในการวิจัยการดูแลสุขภาพในประเทศกำลังพัฒนา

คณะกรรมการชีวจริยธรรมนัฟฟิลด์ (Nuffield Council on Bioethics)

หน้าว่าง

คณะกรรมการ Nuffield Council on Bioethics

Professor Sir Ian Kennedy - ประธาน

Professor Martin Bobrow CBE - รองประธาน

กรรมการ

Professor Tom Baldwin

Professor Sir Kenneth Calman KCB FRSE

The Rt Rev Richard Harries DD FKC FRSL

Professor Bob Hepple QC

Mrs Rebecca Howard

Professor John Ledingham

Professor Catherine Peckham CBE

Professor Martin Raff FRS

Mr Nick Ross

Professor Hebert Sewell

Professor Dame Marilyn Strathern FBA

Professor Albert Weale FBA

Dr Alan Williamson FRSE

สำนักงานเลขานุการ

Dr Sandy Thomas (ผู้อำนวยการ)

Ms Susan Bull (ผู้ช่วยผู้อำนวยการ)

Ms Tor Lezmore (ผู้ช่วยผู้อำนวยการ)

Mrs Julia Fox

Ms Yvonne Melia

Ms Nicola Perrin

Ms Amanda Jones

Ms Maria Gonzales-Nogal

Mrs Elaine Talaat-Abdalla

ขอบเขตงานของคณะกรรมการ

1. เพื่อระบุและทำให้คำถามเกี่ยวกับจริยธรรมซึ่งเกิดขึ้นจากความก้าวหน้าในการวิจัยทางชีววิทยาและการแพทย์มีความชัดเจน ทั้งนี้เพื่อตอบสนองและคาดการณ์ความสนใจของสาธารณชน
2. เพื่อจัดการตรวจสอบและรายงานคำถามดังกล่าว ด้วยมุมมองที่มุ่งส่งเสริมความเข้าใจและการอภิปรายในวงกว้าง ซึ่งอาจนำไปสู่การกำหนดแนวทางใหม่ๆ ตามความจำเป็นโดยมีองค์กรควบคุมกำกับหรือองค์กรอื่นที่เหมาะสมมาทำหน้าที่กำกับดูแล
3. จัดพิมพ์และนำเสนอผลงานตามที่คณะกรรมการเห็นว่าเหมาะสม

Nuffield Council on Bioethics ได้รับทุนสนับสนุนจาก Medical Research Council, มูลนิธิ Nuffield (Nuffield Foundation) และ Wellcome Trust

คำนำ

รายงานใดที่เกี่ยวข้องกับการศึกษาวิจัยเกี่ยวกับสุขภาพของมนุษย์ มักเป็นที่สนใจของผู้อ่านในวงกว้าง. สำหรับรายงานฉบับนี้มีวัตถุประสงค์หลักเพื่อพิจารณาการศึกษาวิจัยที่ได้รับการสนับสนุนจากภายนอกเนื่องจากส่งผลกระทบต่อการศึกษาวิจัยที่ดำเนินการในประเทศกำลังพัฒนา รายงานนี้จึงมีขอบเขตกว้างมาก. คณะทำงานได้ประชุมกันเป็นเวลาเกือบสองปี ซึ่งดำเนินมาด้วยความใส่ใจอย่างเต็มที่จากผู้ที่มีส่วนร่วมในการวิจัยในโลกที่กำลังพัฒนา. ประกอบกับความปรารถนาที่จะเห็นการศึกษาวิจัยเกี่ยวกับโรคและความเจ็บป่วยที่มีมาตรฐานสูงสุด เพื่อประโยชน์ของคนไข้ในรุ่นต่อไป และเพื่อการพัฒนาสุขภาพของประชากร

คณะทำงานกำหนดกรอบในการพิจารณาตั้งแต่เริ่มต้น โดยมุ่งประเด็นเกี่ยวกับการบรรลุภาระหน้าที่ทางจริยธรรมในเรื่องความยุติธรรมและความเคารพในบุคคลท่ามกลางปัญหาความยากจน การขาดแคลนทรัพยากรและโอกาสที่จะมีการเอาใจเอาเปรียบ ซึ่งเป็นประเด็นที่ท้าทายผู้ให้การสนับสนุนอย่างชัดเจน. คณะทำงานตระหนักดีว่าปัจจัยต่างๆ เหล่านี้มีส่วนเกี่ยวข้องกับการสาธารณสุข ธรรมภิบาล และการขาดแคลนสิ่งอำนวยความสะดวก และความสัมพันธ์ในบางส่วนของโลก. ประเด็นเหล่านี้ส่วนใหญ่เป็นเรื่องที่เราไม่อาจทำอะไรได้ นอกจากเปิดเผยถึงความกังวลของเรา. อย่างไรก็ตามเราแนะนำอย่างหนักแน่นว่าจะต้องมีมาตรการคุ้มครองที่เหมาะสมบนพื้นฐานของหลักจริยธรรมตามที่เราระบุ เพื่อปกป้องผู้ที่มีส่วนร่วมในการศึกษาวิจัย

การศึกษาวิจัยเกี่ยวกับการดูแลสุขภาพเป็นประเด็นที่ถกเถียงกันอย่างเผ็ดร้อนในช่วงไม่กี่ปีที่ผ่านมา และเป็นเรื่องที่มีการรายงานและการสืบสวนในหลายกรณี. รายงานนี้จึงถือเป็นส่วนหนึ่งของการถกเถียงซึ่งมุ่งเน้นที่การศึกษาวิจัยในประเทศกำลังพัฒนาที่ได้รับการสนับสนุนจากภายนอก. คณะทำงานพยายามค้นหาข้อมูลอย่างรอบด้าน และเข้าไปในพื้นที่ต่างๆ เกือบทั่วโลกเพื่อสืบหาข้อเท็จจริง. คณะทำงานเองประกอบด้วยสมาชิกจากหลายชาติ เราจึงเตือนตัวเองตลอดเวลาว่าการพิจารณาประเด็นเกี่ยวกับจริยธรรมนั้นสามารถทำได้หลายวิธี. ดังเช่น ความแตกต่างทางวัฒนธรรม สังคม และศาสนา ซึ่งเป็นส่วนหนึ่งของบริบทที่เราศึกษา. ด้วยเหตุนี้เราจึงพิจารณาประเด็นนี้จากมุมมองของประชากรหรืออาสาสมัครวิจัย. เราหวังว่าการพิจารณาจากมุมมองดังกล่าวจะเป็นหลักประกันว่าการใคร่ครวญอย่างรอบคอบของเราจะทำให้ข้อเสนอแนะของเราได้รับการพิจารณาต่อไป

ข้อเสนอแนะซึ่งปรากฏในรายงานมีความสัมพันธ์กับองค์กร หน่วยงาน และรัฐบาลในประเทศต่างๆ รวมทั้งอาสาสมัครวิจัย. โดยเป็นประเด็นเกี่ยวกับความยินยอม มาตรฐานในการดูแลรักษา การทบทวนด้านจริยธรรม และสิ่งที่ควรปฏิบัติหลังจากสิ้นสุดการศึกษาวิจัย. ทั้งนี้คณะทำงานหวังว่าข้อเสนอแนะเหล่านี้จะมีการถกเถียงและนำไปพิจารณา. ซึ่งเราตั้งใจว่าจะทบทวนผลตอบรับที่มีต่อรายงานนี้ภายในสิบแปดเดือน

ข้าพเจ้าขอขอบคุณสมาชิกในคณะทำงานซึ่งทำงานอย่างหนักและกระตือรือร้น เราทำงานร่วมกันเป็นทีมได้เป็นอย่างดี. ข้าพเจ้าขอขอบคุณ Dr. Sandy Thomas ผู้อำนวยการ Nuffield Council on Bioethics เป็นพิเศษสำหรับการให้ความสนับสนุนทั้งปวงต่อคณะทำงาน และทำให้เรามุ่งมั่นทำงานจนลุล่วง. ขอขอบคุณ Julia Fox, Yvonne Melia และ Tor Lezmore สำหรับความช่วยเหลือทุกอย่าง. และที่ต้องขอบคุณเป็นพิเศษคือ Suzan Bull สำหรับการทำงานอย่างไม่เห็นแก่เห็นดีเห็นน้อย นอกจากนี้อารมณ์ดีของเธอยังช่วยให้รายงานนี้สำเร็จลุล่วงไปได้ด้วยดี. ข้าพเจ้ารู้สึกมีเกียรติอย่างยิ่งที่ได้เป็นประธานคณะทำงาน และหวังเป็นอย่างยิ่งว่ารายงานนี้จะกระตุ้นให้เกิดการแลกเปลี่ยนและถกเถียงในประเด็นต่างๆ ที่ควรค่า

เคนเน็ท ซี คาลแมน

กิตติกรรมประกาศ

คณะทำงานใคร่ขอขอบคุณองค์กรและบุคคลต่างๆ ที่มีส่วนช่วยในการทำรายงานนี้ โดยเฉพาะอย่างยิ่งผู้ที่เข้าร่วมประชุมเพื่อสืบหาข้อเท็จจริงหรือให้คำปรึกษา. และขอขอบคุณผู้ที่ให้คำแนะนำในหัวข้อเฉพาะตามที่คณะทำงานร้องขอ. อีกทั้งขอขอบคุณนายแพทย์วิชัย โชควิวัฒน์ Dr. Soledad Diaz, ศาสตราจารย์ Sir Colin Dollery, Dame Rennie Fritchie DBE, ศาสตราจารย์ Helen Lambert, ศาสตราจารย์ Adetokunbo Lucas, ศาสตราจารย์ Ruth Macklin, Dr. Vasantha Muthuswamy และ Baroness Onora O'Neill ซึ่งช่วยตรวจทานร่างฉบับแรกๆ ของรายงานนี้. ความเห็นของท่านเหล่านี้ซึ่งมีคำวิจารณ์ที่ทั้งกว้างไกลและลงรายละเอียดเป็นประโยชน์อย่างยิ่ง ซึ่งเราจะพยายามตอบสนองต่อไป

จริยธรรมในการวิจัยการดูแลสุขภาพในประเทศกำลังพัฒนา

รายชื่อคณะกรรมการ

Professor Sir Kenneth Calman (ประธานคณะกรรมการ) รองอธิการบดีและผู้ดูแล มหาวิทยาลัย Durham

Dr. Fred Binka รองศาสตราจารย์ประจำภาควิชาระบาดวิทยา คณะสาธารณสุขศาสตร์ มหาวิทยาลัย Ghana

Professor Michael Elves อดีตผู้อำนวยการสำนักงานกิจการด้านวิทยาศาสตร์และการศึกษา Glaxo Wellcom Plc

Professor V I Mathan ที่ปรึกษาอาวุโสหน่วยวิจัยสุขภาพ สภาวิจัยการแพทย์แห่งอินเดีย สถาบันระบาดวิทยาแห่งชาติ เซนไน อินเดีย

Professor Keith McAdam ผู้อำนวยการห้องปฏิบัติการวิจัย สภาวิจัยการแพทย์ Faraja The Gambia

Dr. Anne McLaren สถาบันเวลล์คัม/CRC Cambridge

Professor Bhikhu Parekh ศาสตราจารย์ประจำศูนย์ศึกษากาการอภิบาลโลก London School of Economics

Professor David Parkin ศาสตราจารย์ประจำภาควิชาสังคมมานุษยวิทยา วิทยาลัย All Souls, Oxford

Professor Catherine Peckham CBE ศาสตราจารย์ประจำภาควิชาระบาดวิทยา สถาบันสุขภาพเด็ก University College ลอนดอน

Professor Povl Riis กระทรวงวิทยาศาสตร์ โคเปนเฮเกน

Professor Nelson Sewankambo คณบดีคณะแพทยศาสตร์ Makerere University, Kampala, Uganda

Mrs Shahwar Sadeque ที่ปรึกษาด้านการศึกษาและเทคโนโลยีสารสนเทศ

Professor Peter Smith หัวหน้าภาควิชาโรคติดต่อเชื้อและโรคเขตร้อน London School of Hygiene and Tropical Medicine

Dr. Fabio Zicker ผู้ประสานงานพัฒนาศักยภาพการศึกษาวิจัย UNDP/ ธนาคารโลก/ โครงการพิเศษเพื่อการศึกษาวิจัยและการฝึกอบรมโรคเขตร้อน องค์การอนามัยโลก (TDR)

จริยธรรมในการวิจัยการดูแลสุขภาพในประเทศกำลังพัฒนา

ขอบเขตของงาน

1. ทบทวนความสำคัญของการวิจัยการดูแลสุขภาพในมนุษย์ ซึ่งทำการวิจัยในประเทศกำลังพัฒนา
– อย่างน้อยก็บางส่วน โดยได้รับการสนับสนุนจากประเทศที่พัฒนาแล้ว
2. ระบุและพิจารณาเรื่องทางจริยธรรมและสังคมของการวิจัยดังกล่าว ในประเด็นต่างๆ ได้แก่
 - ก. ผู้ที่ได้รับประโยชน์จากการวิจัย
 - ข. ความยินยอม ความแตกต่างในคุณค่าทางวัฒนธรรม
 - ค. ความแตกต่างของระดับการดูแลสุขภาพในประเทศต่างๆ
 - ง. ความสอดคล้องกันของแนวทางจริยธรรมซึ่งกำหนดโดยองค์กรสากล
 - จ. ความรับผิดชอบขององค์กรซึ่งทบทวนเกี่ยวกับจริยธรรมในห้องถิ่นและนอกห้องถิ่น และวิธีการทบทวนและกำกับดูแล
 - ฉ. การติดตามผล รวมทั้งการดำเนินการที่เป็นไปได้กับสิ่งที่ค้นพบ หลังจากการวิจัยสิ้นสุด
3. ให้ข้อเสนอแนะ

บทสรุปผู้บริหาร

รายงานนี้จัดทำขึ้นเพื่อตรวจสอบประเด็นเกี่ยวกับจริยธรรมซึ่งถูกหยิบยกขึ้นมา เมื่อมีการวิจัยการดูแลสุขภาพในประเทศกำลังพัฒนา ซึ่งได้รับทุนจากผู้สนับสนุนจากประเทศพัฒนาแล้ว ทั้งนี้ประเทศกำลังพัฒนามีความต้องการการวิจัยอย่างเร่งด่วน เพื่อที่จะแก้ปัญหาภาวะโรคอันหนักหน่วงที่ต้องแบกรับ. การมีทรัพยากรที่ไม่เท่าเทียมกันระหว่างประเทศพัฒนาแล้วกับประเทศกำลังพัฒนาก่อให้เกิดความเสี่ยงจริงต่อการเอาผิดเอาเปรียบในการวิจัยที่ได้รับการสนับสนุนจากภายนอก. ด้วยความตระหนักว่าผู้ให้การสนับสนุนจากภายนอกมีแรงจูงใจที่แตกต่างกันในการทำวิจัยในประเทศกำลังพัฒนา คณะทำงานจึงมีความเห็นว่าทุกประเทศควรจัดลำดับความสำคัญของประเทศในเรื่องการดูแลสุขภาพ. และเมื่อโครงการวิจัยที่ได้รับการสนับสนุนจากภายนอกไม่อยู่ในลำดับความสำคัญของประเทศ การวิจัยนั้นจะต้องได้รับการพิจารณาเหตุผลความจำเป็นโดยคณะกรรมการจริยธรรมการวิจัย. เพื่อการพัฒนาศักยภาพของประเทศกำลังพัฒนาในการทำวิจัยให้สอดคล้องกับความต้องการของแต่ละประเทศนั้น **คณะทำงานมีข้อเสนอแนะว่าควรให้การพัฒนาความรู้ความชำนาญของท้องถิ่นในการจัดการดูแลสุขภาพและการวิจัยการดูแลสุขภาพเป็นส่วนหนึ่งของโครงการวิจัยด้วย**

คณะทำงานตระหนักดีว่าผู้ที่มีส่วนร่วมในการวิจัยซึ่งได้รับทุนจากภายนอก มักต้องเผชิญกับความแตกต่างหลากหลาย รวมทั้งคำชี้แนะที่ก่อให้เกิดความขัดแย้งว่าอะไรเป็นสิ่งที่สามารถยอมรับได้ในทางจริยธรรม. รายงานนี้มีจุดมุ่งหมายที่จะนำเสนอเค้าโครงเกี่ยวกับจริยธรรมซึ่งสามารถนำไปปรับใช้กับคำชี้แนะเหล่านั้นได้ และเพื่อช่วยในการทบทวนจริยธรรมในการศึกษาวิจัยแก่ผู้ที่มีส่วนร่วมในการพัฒนาคำชี้แนะระดับชาติ. เค้าโครงของจริยธรรมที่นำเสนอในรายงานนี้อยู่บนพื้นฐานของหลักการ 4 ประการ ได้แก่ ภาระหน้าที่ในการบรรเทาความทุกข์ทรมาน ภาระหน้าที่ในการแสดงความเคารพต่อบุคคล ภาระหน้าที่ที่ต้องมีความละเอียดอ่อนต่อความแตกต่างทางวัฒนธรรม และภาระหน้าที่ที่จะไม่เอาผิดเอาเปรียบผู้ที่เปราะบาง ทั้งนี้ผู้วิจัยควรปฏิบัติตามหน้าที่สี่ประการนี้โดยเคร่งครัดเวลาวางแผนและดำเนินการวิจัย. คณะทำงานขอเน้นว่าการพิจารณาบริบททางสังคม วัฒนธรรมและเศรษฐกิจ มีความสำคัญอย่างยิ่งเวลานำหลักการนี้ไปใช้. นอกจากนี้รายงานนี้ได้ระบุถึงข้อกำหนดขั้นต่ำสุดที่ต้องปฏิบัติตาม

ความยินยอม

คณะทำงานมีข้อสรุปว่าในบางวัฒนธรรม ก่อนที่จะมีการติดต่อกับอาสาสมัครให้เข้าร่วมการวิจัย ผู้วิจัยอาจสมควรได้รับความเห็นชอบจากชุมชนหรือจากผู้มีอาวุโสในครอบครัวเสียก่อน กระนั้นก็ตามอาสาสมัครผู้เข้าร่วมการวิจัยแต่ละคนจะต้องให้ความยินยอมอย่างแท้จริงที่จะเข้าร่วมการวิจัยด้วยเสมอ

มาตรฐานการดูแลรักษา

คณะทำงานมีข้อสรุปว่าในการกำหนดมาตรฐานการดูแลรักษาที่เหมาะสมซึ่งจัดให้แก่ผู้ที่อยู่ในกลุ่มเปรียบเทียบกับโครงการวิจัย จะต้องปรึกษาหารือกับผู้ทำงานอยู่ในประเทศที่เป็นพื้นที่วิจัยเท่านั้น. จากนั้นจะต้องได้รับการยอมรับจากคณะกรรมการจริยธรรมการวิจัยที่เกี่ยวข้อง. หากเป็นไปได้อาสาสมัครวิจัยซึ่งอยู่ในกลุ่มเปรียบเทียบกับควรได้รับการดูแลตามมาตรฐานสากล¹ (universal standard of care) สำหรับโรคที่ทำการศึกษาวิจัย. แต่ในกรณีไม่เหมาะสมที่จะใช้มาตรฐานดังกล่าว อย่างน้อยที่สุดควรเป็นมาตรฐานการดูแลรักษาที่ดีที่สุดเท่าที่มีอยู่ในระบบสาธารณสุขของประเทศนั้น

หลังจากสิ้นสุดโครงการวิจัย

คณะทำงานมีข้อสรุปว่า การทำวิจัยโดยไม่ตัดสินใจไว้ก่อนว่าอาสาสมัครวิจัยในกลุ่มเปรียบเทียบกับจะได้รับวิธีการดูแลรักษาที่พิสูจน์แล้วว่าได้ผลหลังเสร็จสิ้นการศึกษาวิจัยเป็นสิ่งที่ไม่อาจยอมรับได้. ผู้วิจัยควรมีหลักประกันว่าอาสาสมัครวิจัยทุกคนที่ควรได้รับประโยชน์จากการวิจัยสามารถเข้าถึงวิธีการดูแลรักษาที่พิสูจน์แล้วว่าได้ผลหลังการวิจัยสิ้นสุดลง. นอกจากนี้ผู้วิจัยควรพิจารณาถึงความเป็นไปได้ในการนำไปใช้และคงไว้ซึ่งการรักษาที่ได้ผลในชุมชนที่กว้างขึ้นก่อนเริ่มต้นการวิจัย. หากพิจารณาแล้วว่าไม่สามารถทำได้ ผู้วิจัยจะต้องพิสูจน์ต่อคณะกรรมการจริยธรรมการวิจัยว่าเพราะเหตุใดจึงควรทำวิจัยนั้น

การทบทวนจริยธรรมของโครงการวิจัย

ระบบที่มีประสิทธิผลในการทบทวนความเหมาะสมทางจริยธรรมของการศึกษาวิจัยเป็นมาตรการสำคัญในการปกป้องอาสาสมัครวิจัย. อย่างไรก็ตาม ประเทศกำลังพัฒนาบางประเทศอาจไม่มีระบบดังกล่าวหรือระบบอาจไม่มีประสิทธิผล. **คณะทำงานมีข้อเสนอว่าทุกประเทศควรสร้างระบบที่มีประสิทธิผลในการทบทวนจริยธรรมในการศึกษาวิจัย ซึ่งรวมถึงการจัดตั้งและคงสถานะของคณะกรรมการจริยธรรมการวิจัยซึ่งเป็นอิสระจากรัฐบาลและผู้ให้ทุน.** โครงการวิจัยควรจะต้องมีการทบทวนด้านจริยธรรมทั้งในประเทศที่ทำวิจัยและประเทศที่ให้ทุนวิจัย. คณะทำงานยินดีที่จะเห็นการริเริ่มการจัดตั้งคณะกรรมการจริยธรรมการวิจัย และฝึกรวมสมาชิกที่เป็นคณะกรรมการ รวมทั้งการกำกับดูแลการพัฒนาของคณะกรรมการโดยหน่วยงานระดับสากล. ทั้งนี้ประเทศที่สนับสนุนการวิจัยในประเทศกำลังพัฒนาควรให้ทุนสำหรับการดำเนินการดังกล่าว. นอกจากนี้คณะทำงานขอเสนอว่าผู้ให้ทุนระดับชาติและนานาชาติควรแน่ใจว่าการฝึกรวมเรื่องจริยธรรมในการศึกษาวิจัยแก่บุคลากรในสาขาวิชาชีพต่างๆ ที่มีส่วนร่วมในการวิจัยอย่างเพียงพอ

¹ เราใช้คำว่า “มาตรฐานการดูแลรักษาสากล” เพื่อบ่งชี้ถึงวิธีการรักษาโรคหรืออาการเจ็บป่วยที่ดีที่สุดที่มีอยู่ไม่ว่าจะที่ไหนในทุกประเทศทั่วโลก

จรรยาบรรณในการวิจัยการดูแลสุขภาพในประเทศกำลังพัฒนา

สารบัญ

สมาชิกของคณะกรรมการและขอบเขตงาน	I
คำนำ	III
กิตติกรรมประกาศ	V
รายชื่อคณะทำงาน	VI
ขอบเขตงานของคณะทำงาน	VII
บทสรุปผู้บริหาร	VIII
หมวดที่ 1 บทนำ	1
บทที่ 1 คำนำ	1
ขอบเขตของรายงาน	1
ความเป็นมา	2
ความยินยอม	3
มาตรฐานการดูแล	5
การทบทวนจรรยาบรรณในการวิจัย	7
เกิดอะไรขึ้นเมื่อการวิจัยสิ้นสุดลง	7
หมวดที่ 2 บริบท	9
บทที่ 2 การดูแลสุขภาพ : บริบททางเศรษฐศาสตร์	9
บทนำ	9
ความแตกต่างของอายุคาดในประเทศต่างๆ	10
ความแตกต่างของทรัพยากรในการดูแลสุขภาพในประเทศต่างๆ	14
ภาวะไร้ดุลยภาพ 10/90 : งบวิจัยและการตายก่อนวัยอันควร	19
ขอบเขตของการวิจัยที่ได้รับการสนับสนุนจากภายนอก	20
การกำหนดลำดับความสำคัญของการศึกษาวิจัย	24
การวิจัยและพัฒนา (R&D) ในประเทศกำลังพัฒนา	31
การพัฒนาวิธีการใหม่	35
อนาคต	41
บทที่ 3 ประเด็นทางสังคมและวัฒนธรรม	43
บทนำ	43
ความแพร่หลายของระบบการแพทย์ทางเลือก	44
การผสมผสานการดูแลสุขภาพแผนปัจจุบันกับการแพทย์ดั้งเดิม	44
ทัศนะเกี่ยวกับความเจ็บป่วย โรค เคราะห์ และความตาย	46

	ความสัมพันธ์ระหว่างแพทย์กับผู้ป่วย : ผู้เชี่ยวชาญกับผู้รับการเชี่ยวชาญ	48
	การให้ข้อมูลเกี่ยวกับการวิจัยแก่อาสาสมัครวิจัย	50
	การตัดสินใจเกี่ยวกับการวิจัย	51
บทที่ 4	เค้าโครงของจริยธรรม	56
	บทนำ	56
	ภาระหน้าที่ในการบรรเทาความทุกข์ทรมาน	58
	การเคารพในบุคคล	59
	ความละเอียดอ่อนต่อความแตกต่างทางวัฒนธรรม	60
	ภาระหน้าที่ที่จะไม่เอาเปรียบผู้เปราะบาง	62
	จากหลักการสู่การปฏิบัติ	63
บทที่ 5	กรอบคำชี้แนะ	64
	บทนำ	64
	บริบททางประวัติศาสตร์	65
	คำชี้แนะสากลในการดำเนินการศึกษาวิจัย	67
	ปฏิญญาเฮลซิงกิ	68
	แนวทางของสภาองค์การสากลด้านวิทยาศาสตร์การแพทย์	72
	แนวทางสากลอื่นๆ	73
	คำชี้แนะระดับชาติสำหรับการศึกษาวิจัย	74
	การบังคับใช้คำชี้แนะ	77
	การฝึกอบรม	79
	การพัฒนาคำชี้แนะระดับชาติ	79
หมวดที่ 3	ประเด็นต่างๆ	81
บทที่ 6	ความยินยอม	81
	บทนำ	81
	ข้อมูลข่าวสาร	82
	ประเด็นที่อาจเกิดขึ้นเมื่อมีการให้ข้อมูลเกี่ยวกับการวิจัยแก่อาสาสมัครวิจัย	84
	ความเข้าใจในข้อมูล	86
	แนวคิดที่ซับซ้อนและแนวคิดใหม่	87
	ความสมัครใจ	89
	ความยอมรับและการมีส่วนร่วมของชุมชน	89
	การปฏิเสธที่จะมีส่วนร่วมในการวิจัย	92
	การโน้มน้าว	93
	การบันทึกความยินยอม	96
	สถานการณ์ที่ไม่เหมาะที่จะใช้ใบยินยอม	98

บทที่ 7	มาตรฐานการดูแลรักษา	101
	บทนำ	101
	คำชี้แนะที่มีอยู่	102
	นิยามวิธีการรักษาที่ดีที่สุดในปัจจุบัน	105
	มาตรฐานการดูแลที่เหมาะสมสำหรับกลุ่มเปรียบเทียบในการวิจัยทางคลินิก	106
	การหลีกเลี่ยงการเอาผิดเอาเปรียบ	107
	ความรับผิดชอบของผู้วิจัยและผู้ให้ทุน	108
	การปฏิบัติที่ไม่ปลอดภัย	109
	ความสำคัญของบริบทของการวิจัย	110
	นิยามการดูแลที่ไม่ใช่ตามมาตรฐานสากล	113
	การเบี่ยงเบนจากมาตรฐานระดับชาติ	115
	การศึกษาวิจัยมาตรการป้องกัน	117
	การดูแลอาการอื่นๆ	118
บทที่ 8	การทบทวนจริยธรรมในการวิจัย	119
	บทนำ	119
	ระดับการประเมิน	122
	ความสอดคล้องกับลำดับความสำคัญของการดูแลสุขภาพ	122
	การทบทวนทางวิชาการ	122
	การทบทวนพิจารณาด้านจริยธรรมของการศึกษาวิจัย	123
	ข้อกำหนดเพื่อการทบทวนพิจารณาโครงการศึกษาวิจัยอย่างมีประสิทธิภาพ	124
	การให้ทุนอุดหนุนอย่างเพียงพอแก่คณะกรรมการด้านจริยธรรมการวิจัย	129
	การทบทวนพิจารณาโครงการศึกษาวิจัยในประเทศผู้ให้ทุนและในประเทศ ซึ่งเป็นสถานที่วิจัย	131
	การพัฒนาศักยภาพสำหรับการทบทวนพิจารณาด้านจริยธรรมของ การศึกษาวิจัย	132
บทที่ 9	เกิดอะไรขึ้นหลังงานวิจัยเสร็จสิ้น	136
	บทนำ	136
	การสานต่อการยกระดับการดูแลสุขภาพ	141
	ผลไม่พึงประสงค์	143
	การขาดเซช	143
	การเฝ้าระวังในระยะยาว	145
	การให้การรักษาต่อหลังจากที่งานวิจัยเสร็จสิ้น	146
	การจัดการให้อาสาสมัครในกลุ่มเปรียบเทียบได้เข้าถึงวิธีบำบัดรักษา	147
	การจัดหาวิธีการบำบัดรักษาให้แก่อาสาสมัครวิจัยเมื่องานวิจัยเสร็จสิ้นลง	149

การจัดหาวิธีบำบัดรักษาให้กับชุมชนภายนอก	150
บทบาทของนักวิจัย	152
บทบาทของผู้ให้ทุน องค์กรระหว่างประเทศ รัฐบาลและองค์กรอื่นๆ	154
การพัฒนาความเชี่ยวชาญการวิจัย	158
หมวดที่ 4 สรุปและข้อเสนอแนะ	160
บทที่ 10 สรุปและข้อเสนอแนะ	160
บทนำ	160
เศรษฐศาสตร์การดูแลสุขภาพ	162
การจัดลำดับความสำคัญของการวิจัย	162
ประเด็นทางสังคมและวัฒนธรรม	163
หลักจริยธรรม	164
เค้าโครงของคำชี้แนะ	165
ความยินยอม	166
มาตรฐานการดูแลรักษา	169
การทบทวนจริยธรรมในการวิจัย	173
สิ่งที่เกิดขึ้นหลังจากการวิจัยสิ้นสุดลง	176
สรุปข้อเสนอแนะ : เค้าโครงสำหรับการดำเนินการในอนาคต	179
อภิธานศัพท์และอภิธานคำย่อ	180



The ethics of research related to healthcare in developing countries

NUFFIELD
COUNCIL ON
BIOETHICS

Published by
Nuffield Council on Bioethics
28 Bedford Square
London WC1B 3JS

Telephone: 020 7681 9619
Fax: 020 7637 1712
Email: bioethics@nuffieldbioethics.org
Website: <http://www.nuffieldbioethics.org>

ISBN 0 9522701 9 6
April 2002

To order a printed copy, please contact the Nuffield Council or visit the website.

© Nuffield Council on Bioethics 2002

All rights reserved. Apart from fair dealing for the purpose of private study, research, criticism or review, no part of the publication may be produced, stored in a retrieval system or transmitted in any form, or by any means, without prior permission of the copyright owners.

Printed by Latimer Trend Group
 Estover Road
 Plymouth PL6 7PY

Cover designed by Geoffrey Wadsley

The ethics of
research related to
healthcare in
developing countries

NUFFIELD
COUNCIL ^{ON}
BIOETHICS

Nuffield Council on Bioethics

Professor Sir Ian Kennedy (Chairman)

Professor Martin Bobrow CBE (Deputy Chairman)

Professor Tom Baldwin

Professor Sir Kenneth Calman KCB FRSE

The Rt Rev Richard Harries DD FKC FRSL

Professor Bob Hepple QC

Mrs Rebecca Howard

Professor John Ledingham

Professor Catherine Peckham CBE

Professor Martin Raff FRS

Mr Nick Ross

Professor Hebert Sewell

Professor Dame Marilyn Strathern FBA

Professor Albert Weale FBA

Dr Alan Williamson FRSE

Secretariat

Dr Sandy Thomas (Director)

Ms Susan Bull (Assistant Director)

Ms Tor Lezmore (Assistant Director)

Mrs Julia Fox

Ms Yvonne Melia

Ms Nicola Perrin

Ms Amanda Jones

Ms Maria Gonzalez-Nogal

Mrs Elaine Talaat-Abdalla

The terms of reference are as follows:

- 1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;
- 2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;
- 3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

**The Nuffield Council on Bioethics is funded jointly by
the Medical Research Council, the Nuffield Foundation
and the Wellcome Trust**

Preface

Any report which is concerned with the way in which research related to human health is conducted will be relevant to a wide range of audiences. This Report, the main objective of which is to consider externally-sponsored research as it affects those in developing countries, is particularly broad in its scope. The Working Party met for almost two years and was sustained by a passionate concern for people who take part in research studies in the developing world. This was coupled with the complementary wish to see research into disease and illness being undertaken to the highest standards for the benefit of future generations of patients and for the improvement of the health of populations.

Early on the context of the Working Party's deliberations was defined. Fulfilling the moral duties of justice and respect in the face of poverty, a lack of resources and the potential for exploitation, presents distinctive challenges to sponsors. We recognised that many of these concern broader issues of public health, of governance and of a lack of facilities, funding and expertise in some parts of the world. Much of this we could do nothing about, other than express our concerns. However we could, within our remit, strongly advocate that appropriate safeguards, based on the ethical principles we identified, be put in place to protect those who take part in research studies.

Research related to healthcare has been hotly debated in recent years, and has been the subject of several reports and investigations. Our contribution should thus be seen as part of that debate and one which focuses on externally-sponsored research conducted in developing countries. We have consulted widely and made a number of fact-finding visits across the world. The Working Party itself was multinational and we reminded ourselves on a regular basis that there were many different ways of considering an ethical issue. Cultural, social and religious differences were part of the context within which we worked. We have therefore considered the issues from the point of view of a population or of a research participant who is being studied in a particular context. We hope that this will ensure that the breadth of our thinking will assist in the recommendations being taken forward.

The recommendations are relevant to a wide range of organisations, agencies and national governments, as well as to research participants themselves. They concern issues of consent, standards of care, ethical review, and what should be done once the research is completed. We hope that they will be widely debated and taken up. We intend to review the response to the Report in 18 months' time.

I should like to thank the members of the group for their hard work and enthusiasm, we worked well as a team. I would particularly like to thank the Director of the Nuffield Council on Bioethics, Dr Sandy Thomas for all her input into the work of the group and for keeping us on the straight and narrow. To Julia Fox, Yvonne Melia and Tor Lezemore for all they contributed. Special thanks however must go to Susan Bull, whose tireless work and good humour helped us to get to the end of the Report with style and with a sense of achievement. It has been a privilege to chair the Working Party and I hope that the Report will stimulate the discussion and debate which the issues deserve.



Kenneth C Calman.

Acknowledgements

The Working Party wishes to thank the many organisations and individuals who have assisted its work, particularly those who attended fact-finding meetings or submitted consultation responses. It would also like to thank those who responded to the Working Party's requests for advice on specific areas of the Report. In addition the Working Party is very grateful to Dr Vichai Chokevivat, Dr Soledad Diaz, Professor Sir Colin Dollery, Dame Rennie Fritchie DBE, Professor Helen Lambert, Professor Adetokunbo Lucas, Professor Ruth Macklin, Dr Vasantha Muthuswamy and Baroness Onora O'Neill, who all reviewed an earlier version of the Report. Their comments, which contained both far-reaching and detailed criticisms to which we have sought to respond, were extremely helpful.

The ethics of research related to healthcare in developing countries

Table of Contents

Council membership and terms of reference	iii	
Preface	v	
Acknowledgements	vi	
Working Party membership	xi	
Working Party terms of reference	xiii	
Executive summary	xv	
Section 1	Introduction	1
Chapter 1	Introduction	3
	The scope of the Report	5
	Background	5
	Consent.....	6
	Standards of care	7
	Review of the ethics of research	9
	What happens once research is over?	9
Section 2	The context	11
Chapter 2	Healthcare: the economic context	13
	Introduction	15
	Variations in life expectancy between countries.....	15
	Variation in resources available for healthcare between countries.....	17
	The 10/90 disequilibrium: research expenditure and premature mortality.....	21
	The scope of externally-sponsored research.....	22
	Setting priorities for research.....	24
	Pharmaceutical R&D in developing countries.....	28
	Developing new interventions.....	30
	The future.....	34
Chapter 3	Social and cultural issues	37
	Introduction	39
	Prevalence of alternative medical systems.....	39
	Combining modern healthcare and traditional medicine	40
	Concepts of illness, disease, misfortune and death	40
	The doctor–patient relationship; the healer–client relationship.....	42
	Informing prospective participants about research.....	43
	Decisions about research.....	43

Chapter 4	The ethical framework	47
	Introduction	49
	The duty to alleviate suffering	50
	Respect for persons	51
	Sensitivity to cultural differences	51
	The duty not to exploit the vulnerable	52
	From principle to practice	53
Chapter 5	The framework of guidance	55
	Introduction	57
	The historical context	57
	International guidance for the conduct of research	59
	The Declaration of Helsinki	59
	The CIOMS guidelines	62
	Other international guidance	62
	National guidance for the conduct of research	62
	The enforcement of guidance	64
	Training	65
	The development of national guidance	66
Section 3	The issues	67
Chapter 6	Consent	69
	Introduction	71
	Information	71
	Issues which may arise when informing participants about research	73
	Understanding information	74
	Complex and novel concepts	74
	Voluntariness	75
	The assent/involvement of the community	76
	Refusing to participate in research	77
	Inducements	78
	Recording consent	80
	Situations where consent forms are inappropriate	82
Chapter 7	Standards of care	85
	Introduction	87
	Existing guidance	87
	Defining the best current method of treatment	88
	The appropriate standard of care for control groups in clinical trials	89
	Avoiding exploitation	90
	Responsibilities of researchers and sponsors	90
	Unsafe practices	91
	The importance of the research context	92
	Defining a non-universal standard of care	94
	Deviations from the national standard	95
	Research into preventive measures	96
	Care for other conditions	97
Chapter 8	Ethical review of research	99
	Introduction	101
	Levels of assessment	102

	Relevance to priorities in healthcare	102
	Scientific review.....	102
	Ethical review of research.....	103
	Requirements for effective ethical review of research	103
	Meeting the costs of research ethics committees.....	106
	Reviewing research in the sponsoring country and the country in which the research is conducted	107
	Developing capacity for reviewing the ethics of research.....	108
Chapter 9	What happens once research over?	111
	Introduction	113
	The continuation of improvements in healthcare.....	115
	Adverse effects.....	116
	Compensation	116
	Long-term surveillance	117
	Provision of an intervention once the study is over.....	118
	Providing interventions to the members of control groups	119
	Providing interventions to all the participants in a research project once the study is over.....	120
	Providing interventions to the wider community and beyond	121
	The role of researchers	122
	The role of sponsors, international agencies, governments and other bodies	123
	The development of expertise in research	125
Section 4	Conclusions and recommendations	127
Chapter 10	Conclusions and recommendations	129
	Introduction	131
	Healthcare economics.....	132
	Setting priorities for research.....	132
	Social and cultural issues	133
	Ethical principles	133
	The framework of guidance.....	134
	Consent.....	135
	Standards of care	137
	Ethical review of research.....	140
	What happens once research is over?	141
	Concluding comments: a framework for future action...	143
Appendix 1	Guidance on research related to healthcare	145
Appendix 2	Types of research design	161
Appendix 3	Issues to be considered when reviewing research proposals	165
Appendix 4	Fact-finding meetings	171
Appendix 5	Method of working and consultation	175
Glossary and acronyms		183
Index		199

The ethics of research related to healthcare in developing countries

Members of the Working Party

Professor Sir Kenneth Calman (Chairman) is Vice-Chancellor and Warden, University of Durham

Dr Fred Binka is Associate Professor of Epidemiology, School of Public Health, University of Ghana

Professor Michael Elves is a former Director, Office of Scientific and Educational Affairs, Glaxo Wellcome plc

Professor V I Mathan is a senior Consultant for Health Research, Indian Council of Medical Research, National Institute of Epidemiology, Chennai, India

Professor Keith McAdam is Director, MRC Laboratories, Fajara, The Gambia

Dr Anne McLaren is at the Wellcome/CRC Institute, Cambridge

Professor Bhikhu Parekh is Centennial Professor, The Centre for the Study of Global Governance, London School of Economics

Professor David Parkin is Professor of Social Anthropology, All Souls College, Oxford

Professor Catherine Peckham CBE is Professor of Epidemiology, Institute of Child Health, University College London

Professor Povl Riis is at the Copenhagen Ministry of Science

Professor Nelson Sewankambo is Dean, Faculty of Medicine, Makerere University, Kampala, Uganda

Mrs Shahwar Sadeque is an educational & ICT Consultant

Professor Peter Smith is Head of the Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine

Dr Fabio Zicker is Coordinator, Research Capacity Strengthening, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

The ethics of research related to healthcare in developing countries

Terms of reference

1. To review the importance of healthcare-related research in humans, supported by those in more affluent countries and conducted, at least partly, in developing countries.
2. To identify and consider the ethical and social implications of conducting such research including:
 - (a) who benefits from the research;
 - (b) consent;
 - (c) differences in cultural values;
 - (d) differences in levels of healthcare between countries;
 - (e) compatibility of ethical guidelines produced by international bodies;
 - (f) the respective responsibilities of local and non-local ethics review bodies, and mechanisms for review and monitoring;
 - (g) follow-up, including the possible implementation of findings, after the completion of research.
3. To make recommendations.

Executive summary

The purpose of this Report is to examine the ethical issues raised when research related to healthcare is carried out in developing countries and funded by sponsors from developed countries. Developing countries urgently need research to help to address the enormous burden of disease that they carry. The inequalities in resources between developed and developing countries pose a real risk of exploitation in the context of externally-sponsored research. Recognising that external sponsors differ in their motives for conducting research in developing countries, the Working Party considers that all countries should set national priorities related to their provision of healthcare. When externally-sponsored research is proposed which falls outside the national priorities, its relevance must be justified to the appropriate research ethics committees. To enhance the ability of developing countries to conduct research that is relevant to their needs, **the Working Party recommends that the development of local expertise in the provision of healthcare and in healthcare research should be an integral component of any proposed research.**

The Working Party recognises that those involved in externally-sponsored research are often faced with diverse and sometimes conflicting guidance as to what may be ethically acceptable. This Report aims to present an ethical framework for others to use when applying such guidance and to assist those involved in the development of national guidance for the ethical review of research. The ethical framework proposed in this Report is based on four principles: the duty to alleviate suffering; the duty to show respect for persons; the duty to be sensitive to cultural differences; and the duty not to exploit the vulnerable. It is crucial that these duties are respected when research is planned and conducted. The Working Party emphasises the critical importance of taking into account the context, social, cultural and economic, when applying these principles. Further, it identifies certain minimum requirements that must be met.

Consent

The Working Party concludes that in some cultural contexts it may be appropriate to obtain agreement from the particular community or assent from a senior family member, before any prospective participant in research is approached. However, genuine consent to participate in research must also always be obtained from each participant.

Standards of care

The Working Party concludes that the appropriate standard of care to be provided to members of a control group in a research project can only be defined in consultation with those who work within the country in which the research is to be conducted. It must then be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a universal standard of care¹ for the disease being studied. Where it is inappropriate to offer such a standard, the minimum that should be offered is the best intervention currently available as part of the national public health system.

1 We use the term 'universal standard of care' to indicate the best current method of treatment available anywhere in the world for a particular disease or condition.

Once a research project is completed

The Working Party concludes that it is unacceptable for research to begin without a decision having been made about whether or not participants in the control group will be offered an intervention shown to be successful on completion of the trial. Researchers should endeavour to secure post-trial access to effective interventions for all the participants in a trial who could benefit. In addition, the possibility of introducing and maintaining a successful treatment in the wider community should be considered before research is conducted. If it is thought that this will not be possible, researchers must justify to the relevant research ethics committee why the research should be carried out.

Reviewing the ethics of a research project

An effective system of review of the ethical propriety of research is a crucial safeguard for participants in research. It may, however, be absent or ineffective in some developing countries. **The Working Party recommends that all countries should establish an effective system for the ethical review of research, which includes the establishment and maintenance of research ethics committees that are independent of government and sponsors of research.** Research should be subject to ethical review in both the country(ies) hosting and the country(ies) sponsoring the research. The Working Party welcomes international initiatives for establishing research ethics committees, training their members and monitoring their development. Funding should be provided for these purposes by those who sponsor research in developing countries. **Furthermore, the Working Party recommends that national and international sponsors of research should ensure that adequate provision is made for training of all those professionals involved in research related to healthcare in the ethics of research.**

Introduction

Section 1



Chapter 1

Introduction

4 หน้าว่าง



The scope of the Report

- 1.1 The purpose of this Report is to examine the ethical issues raised when research involving human participants, particularly clinical research, carried out in a developing country¹ is funded or undertaken by agencies or researchers from outside that country. This Report sets out the context in which discussions and decisions about research on healthcare in developing countries take place. It highlights the health problems that are faced on a global scale, the issues which arise when setting national priorities for research related to healthcare and the social and cultural contexts in which research is conducted. The Report sets out a framework for considering the ethical issues raised by externally-sponsored research related to healthcare in developing countries and provides an outline of the current guidelines governing the conduct of such research. It then focuses on the ethical issues which arise in four primary areas: standards of care; consent; review of the ethics of research; and what happens once research is over. In considering these issues solely in the context of research which is externally funded, we do not suggest that the ethical principles which apply to internally-funded, national research are in any way different.
- 1.2 The Working Party was conscious that many of the questions raised in this Report were intimately related to more general issues about economic disparities, injustice, deprivation, and exploitation. Although these broader issues are not addressed in depth, their impact on research related to healthcare and health provision is considered throughout. The Report does not set out guidelines for the conduct of research, but analyses the ethical issues involved in the current debates and recommends ways forward. We hope the Report will make a significant contribution to international debate on these topics and will be of use to those with an interest in this area, including researchers, sponsors and policymakers who will be involved directly or indirectly in research related to healthcare.

Background

- 1.3 Health has many determinants. These include social, cultural, economic, and environmental factors, genetic variation, and the quality of healthcare available. Research into these factors is an essential component of improving health and healthcare in developing and developed countries alike. Basic research into causes of diseases and possible treatments is also vital. The improvement of health worldwide therefore requires a continuing commitment to learn from the results of carefully designed and managed research studies involving individual participants and populations.
- 1.4 In the developing world, research to find new or improved medicines and vaccines is often given high priority. In many circumstances this is appropriate, but research to find better ways of delivering existing products and services to those in need is often equally or more important. Furthermore, 'non-medical' research such as that into provision of improved sanitation, clean water, better nutrition and personal preventive measures may impact on many diseases. The control of HIV infection requires not only research on treatments and potential vaccines, but also studies of behaviour. Thus a spectrum of research may benefit developing countries, ranging from research into genetic determinants of health and disease at one end to pragmatic means of implementing effective treatments at the other.

1 The Working Party debated at length the appropriate terminology to use to distinguish between countries at different levels of economic development, conscious that any classification of countries as 'developed' or 'developing' would be subject to dispute, and to change. It was decided to use the terms 'developed' and 'developing'. While these terms have limitations, they also have a certain currency and are generally understood.



- 1.5 Eighty percent of the world's population lives in developing countries, where both healthcare and research related to healthcare are severely constrained by limited financial and human resources, and by the lack of appropriate infrastructure to deliver healthcare. The imbalance between the need for means of prevention and treatment of disease and the ability to meet these needs is widely recognised. Research related to healthcare carried out in developing countries, often sponsored by developed countries, has made many outstanding contributions to the understanding, prevention and treatment of disease. This is not a recent phenomenon: research on diseases such as malaria, yellow fever and sleeping sickness has been carried out in what are now regarded as developing countries for more than a century.
- 1.6 An increasing amount of research related to healthcare is being supported in developing countries by governments, government agencies and voluntary organisations in developed countries, in addition to international bodies such as the World Health Organization (WHO) and multinational pharmaceutical companies. While some forms of sponsorship have been altruistic, others have been driven by academic interests which may not reflect national priorities for research in the country in which the research is to be conducted (see Box 2.6) or by economic considerations related to the marketing of healthcare products.
- 1.7 Wherever research is conducted, not only should the quality of the research be the same, but the value and respect given to participants in research should be equal. In developing countries the social, cultural and economic contexts in which research is conducted often differ from those in developed countries. Although there is broad agreement about the general ethical principles which apply to research related to healthcare, namely the duty to alleviate suffering, respect for persons, sensitivity to cultural differences and the duty not to exploit the vulnerable, there has been wide debate about the application of these principles in different research settings. Although the various international guidelines on research related to healthcare have provided some broadly based guidance, they have proved to be somewhat difficult to reconcile and apply in practice.
- 1.8 These difficulties were highlighted by the international controversy about a series of clinical trials into the prevention of mother-to-child transmission of HIV in 1997 (see Box 1.2). A deeper ethical analysis is therefore required not only to resolve inconsistencies in the guidance but to contribute to an improvement in practice. The most controversial aspects of research relating to healthcare in developing countries concern the process of consent to participate, the 'standard of care'² which is provided to participants in research and what happens once the research is over.

Consent

- 1.9 If research on healthcare is to be ethically acceptable, participants should be given the relevant information in a comprehensible manner, and must freely consent to take part. This is particularly important in developing countries where many participants consent to research because they believe it is their only means of receiving healthcare or other benefits. The procedures for consent that are used in developed countries may be ineffective or inappropriate in some developing countries because of differences in social and cultural environments. For example, participants in research may feel much more able to discuss research and ask questions within a meeting of the local community than on a one-to-one basis with researchers. In some regions, individuals may feel unable to refuse to participate in research that their elders, family members or community have assented to.

2 We are using the term 'standard of care' to mean the nature of the care and treatment that will be provided to participants in research.



- 1.10 The securing of genuine consent may also be complicated when communities in which research is to be conducted lack familiarity with the basic concept of medical research. Particular difficulties may arise when consent needs to be recorded in illiterate populations. The application of safeguards to protect such participants from possible exploitation is illustrated by the trial of vaccines for leprosy in Box 1.1. In some regions, participants may be unwilling to sign consent forms in the belief that they are signing away rights, or that other adverse repercussions may follow, such as stigmatisation following a positive HIV test (Box 1.1).

Standards of care

- 1.11 Much recent controversy has focused on the level of care provided to the control group in clinical trials. Should the control group receive the best current treatment available anywhere in the world, or treatment based on an alternative standard of care which takes local circumstances into account, such as the best treatment currently available in the country in which the research is being conducted? Where the best current treatment is inexpensive and simple to deliver, the answer is clear. However, in many circumstances the best current treatment available anywhere in the world may be very difficult to provide in developing countries. International attention was focused on this issue in 1997 when US-sponsored research into means of preventing mother-to-child transmission of HIV in Thailand was criticised as being unethical. The research used a locally-relevant standard of care (the control group received a placebo³) which would not have been acceptable if the research had been conducted in the US (see Box 1.2).

BOX 1.1 Towards an appropriate consent process: research into leprosy in Venezuela

In one study of a vaccine against leprosy carried out in rural Venezuela, researchers and prospective participants had no previous experience of an informed consent procedure. A process was designed in which the principal researcher visited communities where the research was to be conducted and explained it to community leaders. Following the approval of the community leaders, the research was explained to the community, followed by a question and answer session.

One to two months later members of the Ministry of Health visited the communities and asked individual participants if they understood what the research was about and whether or not they wished to participate. As many participants were not literate, their decision was recorded by a government worker, or in the presence of such a worker, without any of the researchers being present. Individual decisions were recorded and each participant either signed a form or gave a fingerprint.¹

Written consent and confidentiality: HIV research in the Ivory Coast

A recent research programme which investigated possible methods of reducing mother-to-child transmission of HIV in the Ivory Coast, experienced low participation rates because of the requirement for HIV testing of pregnant women. This reluctance to be tested was due in part to the fear of social exclusion should relatives and, in particular, a husband or partner, become aware of a positive test result. The requirement for written consent to allow the HIV tests to be carried out led to considerable concern about breaches of confidentiality and subsequently, low participation rates.²

- 1 Bloom B (2001) Personal communication, Harvard School of Public Health and Convit J, Sampson C, Zuniga M, Smith PG, Plata J, Silva J *et al* (1992) Immunoprophylactic trial with combined Mycobacterium leprae/BCG vaccine against leprosy: preliminary results, **The Lancet**, 339(8791) 446-50.
- 2 Coulibaly D, Msellati P, Dedy S, Wellfens-Ekra C and Dabis F (1998) Attitudes and behavior of pregnant women towards HIV screening in Abidjan (Ivory Coast) in 1995 and 1996, **Santé**, 8(3) 234-8.

3 A placebo is a treatment known to be without effect, usually used as a control to be compared against a potentially effective substance or method which is being subjected to clinical trial.



BOX 1.2 Standards of care

Research to prevent perinatal transmission of HIV in 1997

In September 1997, a paper by Lurie and Wolfe¹ and an editorial by Angell in the *New England Journal of Medicine*,² and an editorial in *The Lancet*³ criticised placebo-controlled trials of short-course zidovudine given to HIV-infected pregnant women to prevent mother-to-child HIV transmission. The trials, some of which were conducted under the aegis of the Joint United Nations Programme on HIV/AIDS (UNAIDS), WHO, Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH), were designed to determine whether relatively affordable and more feasible shorter courses of zidovudine given to pregnant women in developing countries would reduce the risk of mother-to-child transmission. They were conducted in countries where conventional local pregnancy care did not include antiretroviral treatment. The trial designs had been approved by ethics committees in the countries in which the trials were conducted.

Longer, more expensive and complex courses of zidovudine had been shown to reduce mother-to-child transmission rates in a trial conducted in the US and France.⁴ Research in which the control group would be provided with a placebo would be deemed unethical in developed countries where antiretroviral treatment is available, following demonstration of the effectiveness of long-course zidovudine. The critics of the trials of a short course of treatment argued that it was unethical to give the control group a placebo when it has already been demonstrated that the longer courses reduced transmission of the virus.

Cerebro-spinal meningitis: standard of care in vaccine trials

Cerebro-spinal meningitis (CSM) occurs in epidemic form in parts of West Africa, causing thousands of deaths in epidemic years. One approach to controlling the disease is to develop an effective vaccine. Such a vaccine would need to be tested to determine whether it was effective and possible to deliver in those parts of West Africa with epidemic CSM.

In Africa, in epidemics of CSM, hundreds or thousands of people with signs of meningitis need to be diagnosed by lumbar puncture and treated by injections or antibiotics. One dose of treatment⁵ may then be sufficient and the epidemic may be managed in an open area or school building. In contrast, in developed countries a case of CSM might be admitted to an intensive care facility.

Some might argue that for a trial of a CSM vaccine in a developing country, those in the trial should be provided with the best available treatment if they contract the disease, including admission to an intensive care facility where necessary. However, it would not only be very costly but also probably impractical to make such care available. If it is unethical to conduct research into a vaccine for CSM without a 'universal' standard of care being available, it is unclear where, in Africa, such research could be conducted.

- 1 Lurie P, Wolfe SM (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries, *New England Journal of Medicine*, 337(12): 853-6.
- 2 Angell M (1997) The ethics of clinical research in the third world, *New England Journal of Medicine*, 337(12): 847-9.
- 3 Editorial (1997) The ethics industry, *The Lancet*, 350: 897.
- 4 Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ *et al* (1994) Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Paediatric AIDS clinical trials group protocol 076 study group, *New England Journal of Medicine*, 331(18): 1173-80.
- 5 Such as oil-based chloramphenicol.

- 1.12 Other issues we address in the Report are the standard of care that should be provided to participants in a trial of a preventive intervention, such as a vaccine, who become infected with the disease against which the vaccine was designed to protect. We also consider the responsibility researchers have for those participants who become ill during the research with a disease which is unrelated to the disease being studied.



Review of the ethics of research

- 1.13 Effective review of the ethics of scientific and medical research is essential to ensure that unethical research is not permitted. Notwithstanding that the integrity of the researcher is of critical importance, the accepted method of ensuring that unethical research is prevented is through the establishment of a system in which research ethics committees undertake independent review of scientific protocols. In developed countries and a number of developing countries, such review is a prerequisite for research involving human participants. However, properly functioning research ethics committees are often absent or under-resourced in developing countries. In addition there may not be a pool of sufficiently trained and independent personnel to serve on a committee, and committees may not have the resources required to cover their administrative costs.

What happens once research is over?

- 1.14 Not all research projects will have results that can be translated directly into practice: research into the natural history of a disease, or the progression of an illness, may not have any immediate practical application. Trials of a medicine may reveal that it is not as effective as expected, or is unsafe, and therefore unsuitable for general use. However, research related to healthcare is usually designed to obtain results that will lead to an improvement in the prevention, diagnosis, treatment, or cure of a disease. One issue that arises when considering whether it is appropriate to conduct a specific research study within a developing country is whether the intervention being studied is likely to be affordable in that country if it is shown to be effective. This will often not be a straightforward issue: as noted in Box 1.3, expensive interventions that may appear too costly to implement in a poor country may become affordable within a short period of time while relatively affordable interventions may still be difficult to implement. Furthermore, interventions involving expensive equipment (such as magnetic resonance imaging (MRI) scanners), highly trained personnel (such as surgeons) or large numbers of trained staff (as in some counselling programmes for sexually transmitted diseases (STDs)) are unlikely to undergo such rapid and substantial reductions in cost.⁴

- 1.15 Issues we discuss in the Report include whether it is acceptable to conduct research if the benefits of that research will not be made available to the community in

BOX 1.3 After research is over: hepatitis B vaccination

At the time of a large-scale trial of a hepatitis B vaccine conducted in The Gambia (performed with vaccine donated by the manufacturer), the market price of vaccine was about US \$60 per course (or US \$20 per dose). However, within a few years the market price for developing countries had dropped to approximately US \$1–2 per course bringing it much closer to the price that many such countries could afford.

Hepatitis B vaccine has since been introduced successfully on a national basis in The Gambia and Taiwan and has been demonstrated to induce strong and long-lasting protection against the hepatitis B carrier state (the major precursor of liver cancer). These developments have provided a very strong stimulus to find cheaper ways of producing the vaccine and for the introduction of this vaccine into the childhood immunisation programmes of many developing countries.

4 A recent commentary in **The Lancet** noted that social programmes such as HIV Voluntary Counselling and Testing (VCT) had been given low priority in developing countries because of their high requirements (particularly in cost-terms) on logistics and skills. However, research in the same edition of the journal found such programmes to be comparable in cost to a number of existing interventions for HIV. See Van de Perre P (2000) HIV voluntary counselling and testing in community health services, **The Lancet**, 356(9224) 86–7.



which the research was undertaken. We also consider where the responsibility for making a successful intervention generally available belongs and what role, if any, the researchers and sponsor have. In the case of participants in research who have chronic diseases such as HIV/AIDS, we address who has responsibility for providing continuing care after the research study is completed and what the standard of care should be.

The context

Section 2

12 หน้าว่าง



Chapter 2

Healthcare: the economic context

14 หน้าว่าง



Introduction

- 2.1 The great disparities between levels of health across the world correlate in general quite closely with the degree of socio-economic development of different countries. Not surprisingly, people living in poorer countries tend to have significantly higher rates of morbidity¹ and mortality than those living in wealthier countries. Historically, in the developed world, improved levels of health have been closely correlated with social and economic development.² In the more recent past, the same has held true in countries that are still classed as developing, and this relationship is likely to continue to hold in the future. However, certain countries or regions, such as Sri Lanka, Cuba and some states in India, have achieved improvements in health disproportionate to the development of their economy. This is usually because of the healthcare and educational systems adopted as a result of specific government policies.
- 2.2 Research into the diseases affecting developing countries has to be seen within the context of their socio-economic conditions. Many would regard the wide disparities in wealth between countries, and often between different groups within countries, as inherently unethical and consider that redressing these imbalances should be given a high priority. It is highly likely that a more equitable distribution of resources (wealth) would lead to much greater equality in the health status of different populations. However, some medical or health-related interventions that will improve health status, including vaccines against important infectious diseases such as AIDS, TB and malaria, could be deployed in advance of economic development, and may even promote such development.
- 2.3 However, it would be inappropriate to introduce or promote new interventions in developing countries without prior research into the risks and benefits for the populations in those countries. Even interventions that have been shown to be effective in specific populations will need to be carefully evaluated before being introduced into other areas where the local environmental, ecological and genetic profiles are very different. This kind of research in healthcare is an important priority for developing countries to assist in the proper selection and use of disease-reducing interventions and often needs to be conducted in the country where use of the intervention is proposed. Such research is often expensive and one form of assistance that several developed countries give to developing countries is the funding and provision of scientific and technical support to help promote and foster the conduct of appropriate research.
- 2.4 In this chapter we first review the disparities in the levels of health between countries and then describe the variation in the resources they have available for healthcare and promotion. Against this background we then discuss the measures involved in developing interventions for preventing or treating disease.

Variations in life expectancy between countries

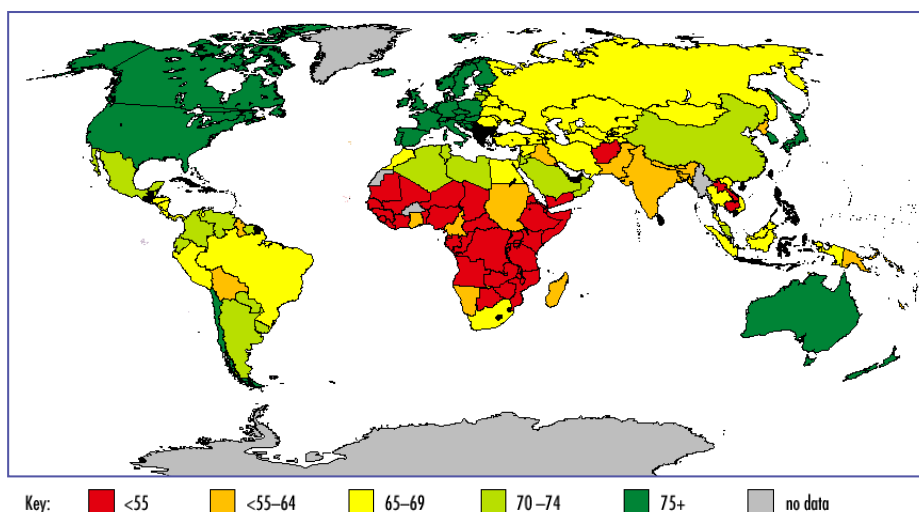
- 2.5 The wide disparity in levels of morbidity and mortality between countries can be illustrated by examining the variation in life expectancy at birth. Figure 2.1 is a world map showing the average number of years that a live-born baby might expect to live in different countries.³ Most of those born in the developed world can expect to live in excess of 70 years, whereas in the majority of African countries average life expectancy is less than 55 years, while in others it is less than 40 years (for example Zambia 38.5; Malawi 37.8 and Sierra Leone 34.3).⁴

1 Levels of sickness and ill health.

2 See for example, McKeown T (1976) **The Role of Medicine: Dream, Mirage or Nemesis**, Nuffield Provincial Hospitals Trust, London.

3 Based on estimated age-specific mortality rates in 1997.

4 World Health Organization (2000) **The World Health Report 2000. Health Systems: Improving Performance**, WHO, Geneva.

Figure 2.1:**Global map of expectation of life at birth**

Redrawn from the World Bank Group's web site at: <http://knowledge.worldbank.org/scripts/esrimpa.dll?name=gisonline&cmd=start map&view=21>. (areas that were unclear on the original are shown in black)

- 2.6 In an attempt to include morbidity as well as mortality in a summary measure of health, the World Health Organization (WHO) has calculated the average 'disability-adjusted life expectancy' for 191 countries.⁵ This is most easily understood as the expectation of the total life lived in full health. Thus, it takes account of years lived with sickness and disease by discounting some of that time according to the seriousness of such conditions. The differences between countries based on disability-adjusted life expectancy are even greater than those based on simple expectation of life at birth. The estimates range from 74.5 years for Japan to 25.9 years for Sierra Leone. The majority of developed countries have estimates in excess of 70 years⁶ while many African countries have estimates below 40 years.⁷ Life expectancies in eastern and central Africa are particularly low because of the devastating effects of the current AIDS epidemic. In general, the levels of health in Asia and Latin America are intermediate between, on the one hand, Japan, North America and Western Europe and, on the other hand, Africa. However, the variation between different countries in each of these regions is substantial.⁸
- 2.7 An important reason for the differences in life expectancy is the variation in mortality rates among infants and young children. The scale of these differences is illustrated by infant mortality rates⁹ in a selection of different countries (Figure 2.2). These range from 5/1000 for Japan to 173/1000 in Afghanistan.¹⁰ There are also substantial variations within countries, as for example between the states of Bihar and Kerala in India and between African-Americans and

5 World Health Organization (2000) **The World Health Report 2000. Health Systems: Improving Performance**, WHO, Geneva.

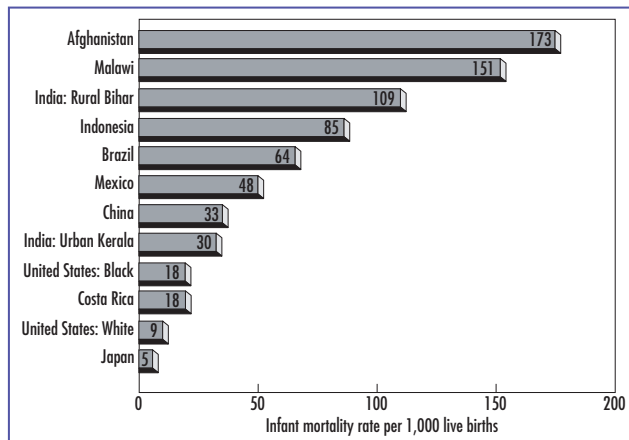
6 For example France 73.1, UK 71.7, US 70 years

7 For example Kenya 39.4, Tanzania 36.0, Zimbabwe 32.9, Uganda 32.7, Zambia 30.3, Malawi 29.4 years.

8 For example, in Latin America disability-adjusted life expectancies range from 68.6 years in Chile, 68.4 in Cuba and 59.1 in Brazil to 53.3 in Bolivia. In Asia, it ranges from 69.3 years in Singapore and 62.8 in Sri Lanka through to 49.5 in Nepal and 37.7 in Afghanistan.

9 The number of children dying in the first year of life, per 1000 children born.

10 Commission on Health Research for Development (CHRD) (1990) **Health Research: Essential Link to Equity in Development**, Oxford University Press, New York.

Figure 2.2:**Infant mortality rate in selected populations**

Reproduced with permission from Commission on Health Research for Development (CHRD) (1990) **Health Research: Essential Link to Equity in Development**, OUP, New York.

whites in the US. Similar variability between countries is evident with respect to child mortality rates, as illustrated in Figure 2.3.¹¹

- 2.8 Much of the difference between mortality rates in developed and developing countries is due to communicable diseases such as AIDS, tuberculosis, malaria, respiratory infections and diarrhoeal diseases. Figure 2.4 shows the disability-adjusted life years (DALYs) lost in three different regions of the world due to communicable diseases, non-communicable diseases and injuries.¹² Nearly three-quarters of the lost DALYs are attributable to communicable diseases in sub-Saharan Africa, compared to only about 10% of lost DALYs in many developed countries.
- 2.9 Until recently, when the effects of the AIDS epidemic began to be reflected in rising rates of mortality, life expectancies had been rising in most countries. They have continued to do so except, generally, in those countries worst hit by the AIDS epidemic, or those in which there has been war. The improvements in life expectancy are likely to be due to improved standards of living and important advances in the development of interventions to prevent or treat disease. The expanded programme of immunisation has been perhaps the most important contributor to lowering infant and child mortality rates. This has raised vaccination rates against some preventable diseases, such as polio and measles, to high levels in many countries. However, for many diseases that cause significant numbers of deaths during childhood, such as malaria, diarrhoeal diseases and respiratory infections, effective vaccines have not yet been developed.

Variation in resources available for healthcare between countries

- 2.10 There is, in general, a strong association between life expectancy and economic development.¹³ Figure 2.5 plots life expectancy at birth in relation to gross national product (GNP) per capita.¹⁴

11 The World Bank (1993) **World Development Report 1993. Investing in Health**, Oxford University Press, New York.

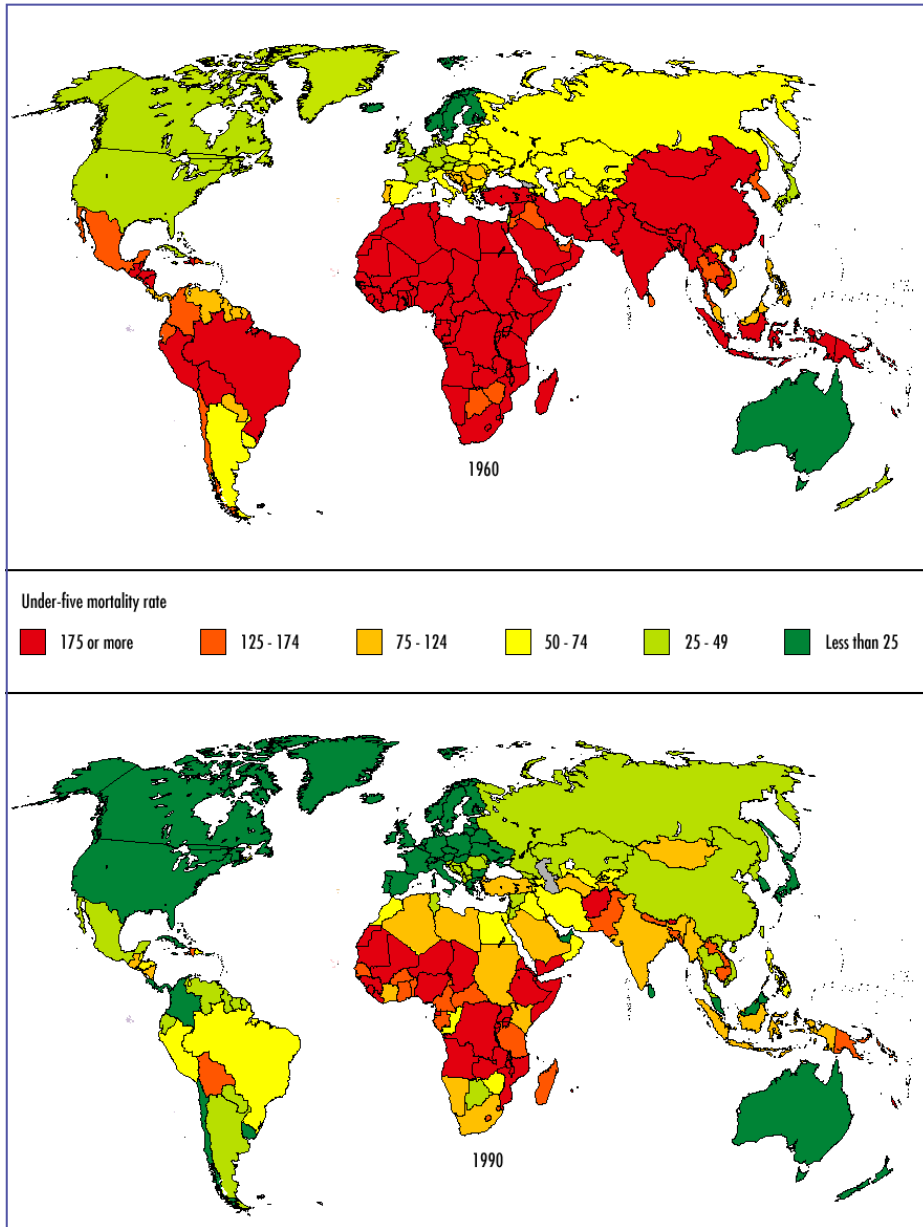
12 The World Bank (1993) **World Development Report 1993. Investing in Health**, Oxford University Press, New York.

13 Commission on Health Research for Development (CHRD) (1990) **Health Research: Essential Link to Equity in Development**, Oxford University Press, New York.

14 The GNP is the total value of all final goods and services produced for consumption in a country: it is a measure of a nation's total economic activity.

Figure 2.3:

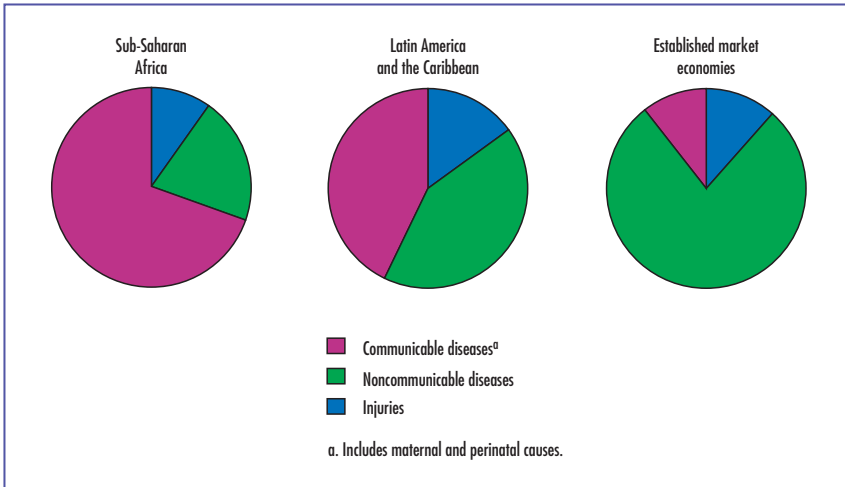
Child mortality by country, 1960 and 1990



Reproduced with permission from The World Bank (1993) *World Development Report 1993. Investing in Health*, Oxford University Press, New York.

Figure 2.4:

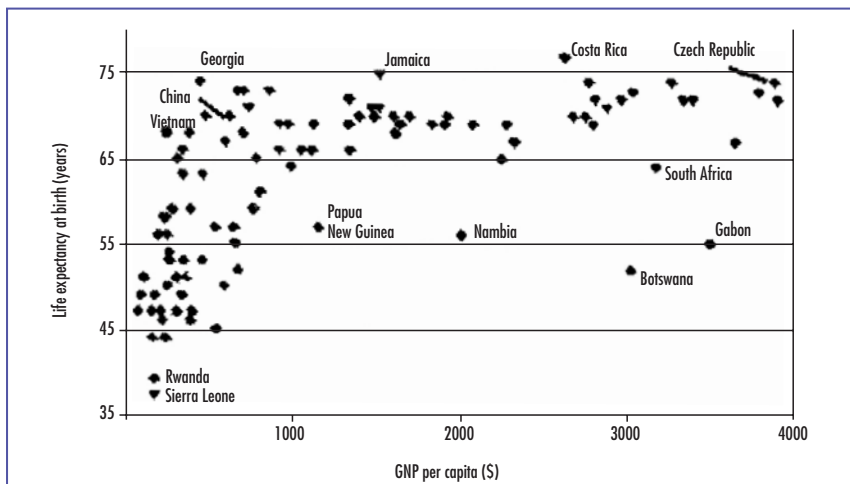
Distribution of disability-adjusted life years (DALYs) lost, by cause, for selected demographic regions, 1990 (percentage of total DALYs lost)



Reproduced with permission from The World Bank (1993) *World Development Report 1993. Investing in Health*, Oxford University Press, New York.

Figure 2.5:

Relationship between life expectancy at birth and gross national product per capita



Reproduced with permission from World Bank Publications.

Table 2.1**Expenditures on health and other health indicators in selected developed and developing countries**

	Annual health expenditure per capita (internat. \$ ¹)	Health expenditure as % GNP	Life expectancy at birth Males/females	Doctors /10 ⁵ popn	Nurses /10 ⁵ popn
United States	3724	13.7	73.8 /79.7	279.0	972.0
Japan	1759	7.1	77.6 /84.3	193.2	744.9
United Kingdom	1193	5.8	74.7 /79.7	164.0	497.0
Chile	581	6.1	73.4 /79.9	110.3	47.2
Brazil	428	6.5	63.7 /71.7	127.2	41.3
Cuba	109	6.3	73.5 /77.4	530.4	677.6
Afghanistan	89	3.2	45.3 /47.2	11.0	18.0
India	84	5.2	59.6 /61.2	48.0	45.0
Sri Lanka	77	3.0	65.8 /73.4	36.5	102.7
Uganda	44	4.1	41.9 /42.4	n/a	18.7
Sierra Leone	31	4.9	33.2 /35.4	7.3	33.0
Somalia	11	1.5	44.0 /44.7	4.0	20.0

Reproduced with permission from WHO (2000) **The World Health Report 2000. Health Systems: Improving performance**. WHO. Geneva and WHO Estimates of Health Personnel: Physicians, Midwives, Dentists and Pharmacists (around 1998) at <http://makeashorterlink.com/?D2271283>.

¹ International dollars' take into account the local purchasing power of the currency and in developing countries are thus generally higher than the expenditure in US\$'s.

Though the relationship is not a simple one, the populations in countries with a low GNP per capita, and especially those with a GNP per capita of less than US\$1000, tend to have much lower life expectancies than those in wealthier countries. Although there has been a substantial improvement in life expectancy over the last several decades in most countries,¹⁵ there has been little change in the relative differences in life expectancy between regions of the world at different levels of economic development, as illustrated in Table 2.1 and Figure 2.6.¹⁶

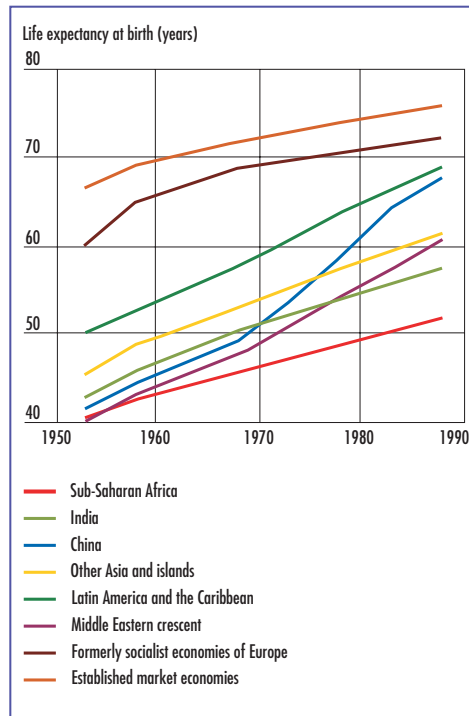
2.11 The previous paragraphs have highlighted the wide differences in health between, and in some cases within, countries and pointed out the broad relationship between better health and more advanced socio-economic development. The level of expenditure that different countries devote to healthcare also varies widely. For example, it has been estimated that the US, which has approximately 5% of the world's population, is responsible for 50% of the annual global expenditure on healthcare.¹⁷ In general, developing countries are able to devote a smaller proportion of their GNP to health than wealthier countries can. Furthermore, in absolute terms, the resources allocated are substantially less than in developed countries. This is reflected in the

15 Before the impact of the AIDS pandemic was reflected in life expectancy data (see paragraph 2.9).

16 The World Bank (1993) **World Development Report 1993. Investing in Health**, Oxford University Press, New York.

17 Bloom B (1999) The future of public health, **Nature**, 402: C63–4.

Figure 2.6:
Trends in Life Expectancy by Demographic Region, 1950–90



Reproduced with permission from The World Bank (1993) **World Development Report 1993. Investing in Health**, Oxford University Press, New York.

numbers of physicians and nurses per member of the population. For example, the number of physicians ranges from over 100 per 100,000 members of the population in more developed countries to less than 10 physicians per 100,000 members of the population in the least developed countries (Table 2.1).

- 2.12 Of course, the health of a population is determined not only by the resources devoted to healthcare and to preventive medicine, but also by investment in other important determinants of good health such as education, nutrition, water, sanitation and communication infrastructure. The lack of resources to develop these facilities, which are crucial if health benefits are to be sustained, further disadvantages developing countries. Even in those countries in which there are potentially more resources available to devote to infrastructure development, political leaders may sometimes have alternative priorities and allocate funds elsewhere.

The 10/90 disequilibrium: research expenditure and premature mortality

- 2.13 The disparity in expenditures on health research between developed and developing countries was highlighted in the 1990 report of the Commission on Health Research for Development.¹⁸ This

18 CHR (1990) **Health Research: Essential Link to Equity in Development**, Oxford University Press, New York.

group assessed the total funds that were being spent on research in different countries and examined the burden of ill health. Their analyses revealed a striking disparity between health needs and research expenditures. Using those countries with the lowest mortality rates as a benchmark, they proposed that differences from these rates in other countries represented potentially avoidable mortality. The amount of avoidable mortality¹⁹ in developed and developing countries was calculated and compared to the estimated research expenditures on the respective health problems of each country. These calculations led to the estimates that 93% of the global burden of premature mortality is attributable to disease problems in developing countries but that about 95% of global expenditure on health research is directed at the disease problems of developed countries. Refinements of these estimates by the WHO Ad Hoc Committee on Health Research²⁰ supported the conclusion that the central problem in research on health is the '10/90 disequilibrium'. Namely, that of the US\$ 50–60 billion spent world-wide each year on health research by both the private and public sectors, only 10% is devoted to the health problems of 90% of the world's population.²¹ It is against such a background that research on health in developing countries must be considered.

- 2.14 The gross disparities in investment in research on health between countries are also reflected in the availability of those with appropriate training to conduct research on health. Despite the great need for research to determine the most effective interventions in developing countries, the indigenous capacity to conduct this research is severely limited. The lack of appropriate infrastructure, expertise and resources are major constraints. Externally-supported research that does not address this issue of development of capacity in research may greatly limit the long-term value of the research. In many respects such research is the equivalent of food aid, which does not provide the tools and skills to help the local population to become self-sufficient in growing their own food. Building capacity within developing countries will help those countries to set their own priorities for research and to conduct the most relevant research for local health needs.
- 2.15 As many developing countries have very limited resources, it is highly desirable that investments in healthcare focus on those interventions that are affordable, effective and accessible. This is best achieved by ensuring, so far as is possible, that health policy is evidence-based: only those interventions that are proven to be effective and affordable are introduced into the national health programme. To develop such an evidence base requires that the experience of other countries with particular interventions is taken into account. When the evidence is lacking, it will sometimes be necessary to conduct new or additional research in the relevant country. This will often be beyond a developing country's own resources and research which is externally sponsored may be the sole means of acquiring the necessary evidence.

The scope of externally-sponsored research

- 2.16 Whilst there is currently no central audit of research which is conducted in developing countries by external sponsors, organisations such as the US Food and Drug Administration (FDA) and Pharmaceutical Research and Manufacturers of America (PhRMA) monitor the amount of research and development (R&D) conducted abroad. The FDA has recorded a 16-fold increase in the number of foreign clinical investigators conducting research on new medicines in the decade 1990–2000. Numbers grew from 271 in 1990 to 4,458 in 1999.²² The number of

19 In terms of years of life lost due to premature mortality.

20 World Health Organization (1996) **Investing in Health Research and Development: Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options**, WHO, Geneva.

21 Global Forum for Health Research (1999) **The 10/90 Report on Health Research 1999**, Global Forum for Health Research, Geneva.

22 DHHS Office of Inspector General (2001) **The Globalization of Clinical Trials. A Growing Challenge in Protecting Human Subjects**, Office of Evaluation and Inspections, Boston.

Table 2.2**Growth in domestic US R&D and R&D overseas**

Year	Domestic US R&D (\$ M)	US R&D Abroad (\$ M)
2001	23,640.0	6,862.0
2000	19,986.7	5,692.2
1999	18,499.3	4,219.6
1998	17,222.5	3,839.0
1997	15,516.6	3,492.1

Source: PhrMA (2001) **Pharmaceutical Industry Profile 2001: Table 1: Growth in Domestic US R&D and R&D Abroad, Ethical Pharmaceuticals, Research-based pharmaceutical companies, 1970–2001.**

countries, monitored by the FDA, in which clinical investigators conducted research increased nearly three-fold from 28 to 79 for the same period, with the largest growth occurring in Latin America and Eastern European countries.²³

- 2.17 In its Annual Survey for 2001, PhRMA gave a detailed account of R&D by research-based pharmaceutical companies. Although this showed recent dramatic growths in the investment and proportion of US R&D conducted abroad (Table 2.2), the proportion of overall R&D conducted in developing countries remains small, with the highest proportion of research carried out in the developing world taking place in Latin America (Table 2.3).
- 2.18 Audits of international research activity on specific diseases have also been conducted. For example, the Unit for Policy Research in Science and Medicine (PRISM) of the Wellcome Trust conducted an audit of malaria research.²⁴ Expenditure dedicated to research on malaria was found to be low compared with other areas of disease. For example, while the UK alone spent over \$200 million on research on cancer in 1993, total expenditure for research on malaria *worldwide* was only \$84 million. Analysis of research publications showed that active research was taking place in many areas of basic research into malaria, such as the mechanisms of action of medicines and disease transmission, but that there was less research in other areas, such as means of providing antimalarial treatment to populations in developing countries.
- 2.19 However, since the second half of the 1990s, this picture of international research activity has been reconfigured somewhat. This is due in part to the growing number of collaborations between the corporate and public sectors in the form of global public-private partnerships (GPPPs). These developed from recognition of market and 'public' failures in international public health and have allowed major investments in the area. Examples include the Medicines for Malaria Venture (MMV), one of the first public-private partnerships which found its origins in the failure of the market system to provide the required incentives for wide-scale R&D in new medicines for malaria.

23 DHHS Office of Inspector General (2001) **The Globalization of Clinical Trials. A Growing Challenge in Protecting Human Subjects**, Office of Evaluation and Inspections, Boston.

24 Anderson J, MacLean M and Davies C (1996) **Malaria Research. An Audit of International Activity**, Unit for Policy Research in Science and Medicine (PRISM), Wellcome Trust, London.

Table 2.3

US funded R&D conducted abroad by geographic area in 1999

Geographic area	Amount (US\$ mil.)	Share (%) ¹
Canada	451.2	9.2
Latin America (inc. all Caribbean nations)	78.5	1.6
Western Europe (EC, European Free Trade Association and Switzerland)	3,569.2	72.9
Central and Eastern Europe (inc. ex-USSR)	21.6	0.44
Middle East (inc. Turkey)	3.5	0.07
Africa	4.1	0.08
Asia/Pacific (from Pakistan to SE Asia inc. China, Taiwan, and the Koreans)	19.7	0.40
Japan	711.1	14.5
Australia and New Zealand	45.4	0.93
Total	4,904.2	

¹Percentages do not add up to 100 because of rounding.

Source: PhrMA (2001) **Pharmaceutical Industry Profile 2001: Table 9: R&D Abroad by Geographic Area, Ethical Pharmaceuticals, Company-financed, U.S.-Owned Research-based Pharmaceutical Companies, 1999.**

2.20 As in developed countries, a very wide range of research related to healthcare is conducted in developing countries, the majority of which is externally sponsored. The spectrum ranges from laboratory research into the causes of disease, through clinical research involving human participants which aims to determine the safety and efficacy of novel interventions, to feasibility and operational research, which is designed to determine if and how effective treatment can be delivered to the broader patient population (see Box 2.1). The various types of research conducted are discussed further in Appendix 2.

Setting priorities for research

2.21 The question of how a country sets its priorities for research in healthcare is particularly important in developing countries because national resources for research are generally very limited. The setting of national priorities for research is a complex process involving national and international research objectives, institutions and individuals. Clearly, the greater the capacity of a country to conduct its own research and to have systems in place to determine its own priorities, the easier it will be to ensure that the questions posed by externally-funded research are appropriate and relevant to national health needs. It will be more difficult for government and external sponsors to collaborate effectively if there is no clear picture of the priorities for research within a country.

2.22 The capacity of developing countries to set their own priorities for research varies widely. Some countries make use of WHO's recommendations by adopting those parts that are relevant to

BOX 2.1 Examples of the kinds of research conducted in developing countries

Basic research

A genetic transformation system for the mosquito *Anopheles stephensi*, a major carrier of malaria in urban areas of the Indian subcontinent has now been developed.¹ Such developments in understanding the interactions between malaria parasites and the mosquito vectors of malaria will allow further research into the molecular aspects of malaria parasite transmission and new control mechanisms for the disease. Researchers at Michigan State University are already investigating the production of genetically engineered strains of mosquito that fail to transmit the pathogen, which may ultimately allow the wild population to be replaced by this 'innocuous' strain.²

Epidemiological research

A study was initiated in the Soroti District of Uganda following an outbreak of *Trypanosoma brucei rhodesiense* sleeping sickness. The disease had previously been absent in the district. However, it coincided with large-scale livestock restocking activities in the area and the research investigated the role of the cattle in the origins of the outbreak, as they can form important reservoirs for the parasite.³ This project was supported by the UK MRC and the DFID Animal Health Programme.

Natural history of diseases

In 2000, the UK MRC funded a 3-year study in north eastern Tanzania. This programme is examining how the pattern of malarial infection is affected by changes in the intensity of malaria transmission due to the effects of altitude on mosquito survival.⁴

Social and behavioural research

Members of the Kigoyera Parish in western Uganda who had undergone HIV testing and counselling were interviewed about their sexual behaviour. This study, which was supported by Germany, was conducted to examine the effectiveness of HIV counselling and testing in reducing high-risk sexual behaviour in this rural population.⁵

Clinical research

The US company, VaxGen is currently conducting a phase III placebo-controlled, double blind trial of its HIV vaccine in Thailand. The participants in research are HIV-negative injecting drug users with a high risk of blood-borne HIV transmission. The trial is designed for a total of 2500 volunteers and is taking place in 17 methadone clinics under the direction of the Bangkok Metropolitan Administration.⁶

Feasibility studies

It was proposed that Zimbabwe adopt a visual inspection with acetic acid (vinegar) as a first line low cost screening method for cervical cancer. A feasibility study was planned in two districts of Zimbabwe to assess the feasibility of integrating the inspection into existing primary health care facilities.⁷ This research was supported by the Ministry of Health of Zimbabwe and the United Nations Population Fund (UNFPA).

BOX 2.1 Continued**Health systems research**

The International Trachoma Initiative (ITI)⁸ is dedicated to eliminating blindness from trachoma. This is a preventive and treatment-based programme, involving the donation of the medicine Zithromax (Azithromycin) and supplemented by surgical techniques and public hygiene education. The programme is then followed up to determine its effectiveness. To date, studies have been conducted in Morocco and Tanzania to assess its success.⁹

- 1 Catteruccia F, Nolan T, Loukeris TG, Blass C, Savakis C, Kafatos FC *et al* (2000) Stable germline transformation of the malaria mosquito *Anopheles stephensi*, **Nature**, 405: 959–62.
- 2 Scientists are racing to create a genetically modified 'super mosquito' that will destroy malaria ..., **Sunday Times**, 1 July 2001.
- 3 See Fevre EM, Coleman PG, Odiit M, Magona JW, Welburn SC and Woolhouse ME (2001) The origins of a new Trypanosoma brucei rhodesiense sleeping sickness outbreak in eastern Uganda, **Lancet**, 358(9282) 625–8.
- 4 See <http://makeashorterlink.com/?C2684108>.
- 5 See Kipp W, Kabagambe G and Konde-Lule J (2001) Low impact of a community-wide HIV testing and counseling program on sexual behavior in rural Uganda, **AIDS Education and Prevention**, 13(3) 279–89.
- 6 See 'VaxGen Clinical Trials' at <http://www.vaxgen.com/vaccine/index.html>.
- 7 http://www.south-south.org/Word_pdf/Sstories/Jinja/cervical%20cancer.pdf.
- 8 The ITI was established by Pfizer Inc. and the Edna McConnell Clark Foundation.
- 9 Access to medicines in the developing world through partnerships, comments by Chuck Hardwick, Senior Vice President, Pfizer Inc., WHO/WTO Workshop on Differential Pricing and Financing of Essential Drugs, 10 April 2001, Høsbjør, Norway.

health policy in their own country.²⁵ Others have used approaches developed over the past decade to systematise the setting of priorities in research on health. The broad aim of these initiatives has been to enable decision makers to make more informed decisions in their allocation of limited research funds. The specific objective has been to ensure that a given investment in research has the greatest impact on the health of the largest number of people in the community. However, many developing countries do not have the resources to make a comprehensive assessment of the prevalence and effects of disease within their borders.

- 2.23 Essential national health research (ENHR) is a strategy which has been used by several developing countries to organise and manage research related to healthcare through systematic priority setting.²⁶ Key criteria for the selection of research areas for priority include economic impact, cost effectiveness of future interventions, effect on equity, social justice and acceptability, and contribution to the strengthening of capacity in research. Some 18 countries have developed ENHR strategies including South Africa, Thailand, Pakistan and Tanzania. The implementation of these strategies will depend on several factors, not least research capacity, the availability of adequate infrastructure and the availability of funding.

- 25 WHO's recommendations about priority areas are formulated by The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), its research programmes and by the Joint United Nations Programme on HIV/AIDS (UNAIDS). More than 50 developing countries have additionally adopted ENHR strategies to support action promoting equity in health. Countries have used a variety of mechanisms to implement the ENHR strategy but which share a common link between research and policymaking. For example, Jamaica has had an ENHR Task Force in place since 1995 which is formally recognised by the Ministry of Health and brings together representatives from the Ministry, university-based units, and the Planning Institute of Jamaica in promoting and advocating ENHR. Uganda has a national task force which consults on research priorities with senior government officials and researchers, district planning committees and health teams, along with community members. In addition, Uganda's ENHR co-ordinating team is trying to develop the capacity to set research priorities and carry out relevant research at the district level, to allow better definition of district-specific problems and the contribution of local communities in determining such. (See Neufeld V and Johnson N (2001) Forging Links for Health Research. Perspectives from the Council on Health Research for Development, International Development Research Center, Canada for further details of country-specific initiatives.)
- 26 The concept of ENHR was advanced by the Commission of Health Research for Development (1990) and its successor, the Task Force on Health Research for Development (1991). The Council on Health Research for Development (COHRED) has further developed the approach through practical application in several countries and provides the current mechanism of support for ENHR at the country and global level.

- 2.24 Overall, progress in implementing strategies for ENHR has been slow and uneven for a number of reasons, including ineffective strategies for communication and weak national funding arrangements. The sociopolitical realities of some countries or parts of countries have also been cited as problematic in establishing effective links between research and policy, whilst international organisations involved in research on health may also significantly influence what happens within a recipient country.²⁷ It has been suggested that these strategies for priority setting have only had an impact in countries such as Thailand where some national funding has been committed to subsequent implementation.²⁸ In countries where nearly all research related to healthcare is externally funded, the priorities for research have been largely set by the external sponsors.
- 2.25 In such circumstances, questions arise about the extent to which external sponsors are guided by national priorities when making decisions about research sponsorship. External agencies, including other national governments, research councils, private sponsors, non-governmental institutions or agencies and pharmaceutical companies, sponsor the majority of research related to healthcare in developing countries. Many funding agencies have their own approaches for the identification of areas which merit support. As many external sponsors fund at the level of individual researchers rather than institutions, it is important that there is awareness of priorities for national research at the local level.
- 2.26 Governmental bodies such as the UK Medical Research Council (MRC) and UK Department for International Development (DfID), US Centers for Disease Control (CDC), the European Commission (EC) (see Box 2.2), international agencies and pharmaceutical companies generally support or undertake applied health-driven research, as do the large charities (for example, the Bill and Melinda Gates Foundation and the Wellcome Trust) (see Box 2.3). Scientific excellence is the first criterion used by most sponsors of research. Additional criteria for funding include the relevance of research to the host countries' needs; the practicalities of undertaking the proposed research; and the likelihood of the research results being taken up in the host country for the improvement of health. Several sponsors have advisory panels with members from both developed and developing countries to assist them in identifying areas of priority for support in consultation with the relevant communities.²⁹
- 2.27 Several GPPPs have also been established to address the public health problems of developing countries, some of which are concerned with research or have a research component.³⁰ Other GPPPs are focused on the development of products such as the International AIDS Vaccine Initiative (IAVI), the Malaria Vaccine Initiative (MVI) and MMV; others are concerned with the donation of specific products such as the Malarone (antimalarial medicine) donation programme or broader programmes as in the Case of Global Alliance for Vaccines and Immunization (GAVI) (see Box 2.4). GPPPs, such as MMV and IAVI, bring together the substantial resources of public and private sector organisations to develop vaccines and medicines for common and serious diseases such as AIDS, TB and malaria.³¹ Research on these diseases will clearly be relevant to the national research priorities of the majority of developing countries.
- 2.28 The United Nations Development Programme/World Bank/WHO 'Special Programme for Research and Training in Tropical Diseases' (TDR) is one of the international agencies that has

27 Chunharas S 'Linking research to policy and action' in Neufeld V and Johnson N (2001) **Forging Links for Health Research. Perspectives from the Council on Health Research for Development**, IDRC, Ottawa.

28 Binka F (2001) Personal communication, Navrongo Health Research Centre.

29 For example, the UK Medical Research Council and the Wellcome Trust.

30 There is some disagreement about what constitutes a public-private partnership but a good definition is thought to comprise three key components: involvement of at least one private profit-seeking organisation with at least one not-for-profit organisation; shared efforts and benefits; commitment to the creation of a social value (improved health), especially for disadvantaged countries. See Reich M (2000) Public-private partnerships for public health, **Nature Medicine**, 6(6) 617-20.

31 Lucas A (2000) Public-private partnerships. Illustrative examples, **Workshop on Public-Private Partnerships in Public Health**, 7-8 April 2000, Endicott House, Dedham, Massachusetts.

BOX 2.2 Examples of governmental bodies funding research in developing countries

UK Medical Research Council (MRC)

The UK MRC works closely with DfID to fund research relevant to priorities in healthcare in developing countries. Research funded ranges from basic to clinical research, with particular emphases given to poverty reduction and the need to foster local capacity in research through in-work training and collaborative partnerships with developing countries. The MRC has laboratories in The Gambia which undertake research programmes spanning HIV/AIDS, TB, malaria, reproductive health, viral diseases, respiratory infections, non-communicable diseases and nutrition, each having basic, clinical and epidemiological components. Additionally, the MRC has an integrated multidisciplinary research programme for the study of HIV-1 in Uganda and a malaria programme in Tanzania. The MRC’s Human Immunology Unit at Oxford University has an established programme for the preparation and trials of HIV vaccines in the UK and Kenya. Phase I trials of a resultant DNA vaccine against HIV are underway in Oxford and Nairobi, Kenya.¹

European Commission Programme of Action to combat HIV/AIDS, malaria and tuberculosis

In February 2001, the EC approved a Communication outlining a programme for action on HIV/AIDS, malaria and tuberculosis which would build on existing EC investments in research on these major diseases.² In terms of research and development, this emphasised targeted action for increased public support for R&D, involving continued and increased support for basic and strategic research with improved co-ordination at European and international levels, along with the creation of a European Clinical Trials platform to increase the number, efficiency and coherence of clinical trials conducted by the public and private sectors, and involving developing countries. Emphasis was also given to developing expertise in research in terms of increasing support to a range of research activities, giving emphasis to gender balance and poverty reduction and ensuring appropriate ethical standards and review systems are in place. Support would also be provided to developing countries to allow them to host and conduct large-scale population trials. The need to develop an incentive package to increase private investment in R&D for new products to tackle major communicable diseases in developing countries was also highlighted.

1 For more detailed information about the MRC’s programmes in developing countries see: <http://makeashorterlink.com/?C2684108>.
 2 See European Commission (2001) **Communication from the Commission to the Council and the European Parliament. Programme for Action: Accelerated action on HIV/AIDS, malaria and tuberculosis in the context of poverty reduction** at <http://makeashorterlink.com/?l66F21E5>.

sought to promote public-private partnerships, and to assist pharmaceutical companies in the late stage of product development. Acting as a broker linking academia, governments, industry, health professionals and affected communities, TDR has been involved in the implementation of field trials and the licensing out of new products, or new uses for existing products.³²

Pharmaceutical R&D in developing countries

2.29 Most of the collaborative research undertaken by pharmaceutical companies in developing countries involves clinical trials. Priorities for national research may be considered to have little

32 Examples are multi-drug therapy for leprosy, ivermectin for onchocerciasis, eflornithine for African trypanosomiasis, artemether for malaria, praziquantel combinations for schistosomiasis and intestinal parasites, and more recently, miltefosine for visceral leishmaniasis, and artesunate suppository, medicine combinations and lapdap for malaria, among others Morel CM (2000) Reaching maturity – 25 years of the TDR, **Parasitology Today**, 16(12) 522–8.



relevance by a company that wishes to test a new medicine. Instead, the criteria for selecting a particular country for trial include the availability of suitable participants, the availability of high quality collaborators, and appropriate infrastructure for delivery of clinical care to the participants. The national priorities for research related to healthcare identified by a host country may have little bearing on where a company decides to locate its clinical trials. However, some companies such as GlaxoSmithKline (GSK) have several R&D projects to develop medicines for the treatment of diseases prevalent in developing countries (see Box 2.5). In some instances, the diseases are also relevant to developed country markets while in others, the research sponsorship may be altruistic.

- 2.30 Where an external agency has its own priorities for research on healthcare, provided that these coincide with those of the recipient country, there is potential for mutual benefit. If the agendas do not coincide, then the financial influence of the external agency may become the driving force (see paragraph 2.24). The principal manner in which a research sponsor might distort the priorities for research in a developing country is through the funding of research that has no direct benefit to its individuals nor to the society as a whole. Examples include the study of the natural history of a disease, a clinical intervention, a diagnostic process or the removal of tissues for research in a developed country. The example of the research on Burkitt's lymphoma in Africa (see Box 2.6) illustrates the issues which can arise when a researcher pursues a study of legitimate interest but which does not address a priority for healthcare in the host country. However, such research can offer considerable indirect benefits to host countries in the developing world because of the potential for strengthening the national capacity in research, in the form of improved infrastructure and training.

- 2.31 Despite the difficulties that developing countries may face in achieving the effective implementation of national priorities for research in healthcare, there is a strong case to be made for setting research priorities together with a robust mechanism for scientific review and ethical review of any proposed research (see Chapter 8). How this is managed will depend on the resources available in each country. **We therefore endorse the view of the Commission on**

BOX 2.3 Examples of charities funding research in developing countries

Bill and Melinda Gates Foundation

In 2000, the Foundation paid and awarded grants totalling US\$1240 million for global health projects. Grants awarded included funding for the development of a vaccine for leishmaniasis, funding for a feasibility study to improve the manufacturing and delivery of vaccines in Russia, support for research aimed at the reduction of child mortality and funding to promote the discovery and development of antimalarial medicines.¹

The Wellcome Trust

The Trust has three international programmes: International Biomedical, Tropical Medicine and Population Studies programmes.² The Trust spent £72.2 million on international research during 1999/2000. This included research into infectious and non-infectious human diseases and veterinary problems affecting developing countries, with research primarily conducted in South-East Asia and Kenya. Several project grants were awarded as part of the Non-communicable Disease Initiative in the areas of mental health, stroke and hypertension in Africa, Latin America and Southern Asia, and additionally, a major programme grant was given in India to explore the role of maternal nutrition and the development of insulin resistance in offspring.³

1 See <http://www.gatesfoundation.org/>.

2 Within its three international programmes, the Trust awarded a variety of fellowships and research and career awards.

3 Material taken from The Wellcome Trust Annual Review 1999/2000 at <http://www.wellcome.ac.uk/en/1/awtpubreparrv00int.html>.

BOX 2.4 Global Alliance for Vaccines and Immunization (GAVI)

GAVI has identified three priorities for its initial vaccine development efforts: pneumococcal conjugate vaccines for pneumonia and meningitis, rotavirus oral vaccines for severe diarrhoea and meningococcal A (or A/C) conjugate vaccines for meningitis. These products were selected because of their potential impact on children's health and because availability and use could be predicted in 5–7 years.¹

1 See http://www.vaccinealliance.org/reference/update_agendas.html for further details about GAVI's agenda to accelerate the development and introduction of these vaccines.

BOX 2.5 GlaxoSmithKline (GSK)

GSK has more than 20 active R&D projects for medicines to treat diseases prevalent in developing countries. It has been researching vaccines for HIV, TB and malaria, has three anti-malarial products at various stages of development and clinical projects are underway with a new combination product and a novel protease inhibitor for HIV/AIDS, along with research efforts to discover medicines with novel mechanisms. GSK has an R&D programme to develop a Hepatitis E vaccine, a disease prevalent in South-East Asia. It also has a randomised clinical trial in children of Zentel (Albendazole) to assess the impact of early de-worming on long-term childhood survival.¹ In addition, GSK has more than 30 external partners and alliances for diseases relevant to developing countries. Paediatric clinical trials of a malaria vaccine began in the Gambia in May 2001 in partnership with MVI. This is the first of a series of three planned trials. GSK is also working in partnership with academic institutions and with NIH funding to identify novel targets for antimycobacterial chemotherapy and developing new compounds suitable for pre-clinical evaluation for TB.²

1 GlaxoSmithKline (2001) **Facing the Challenge. Our contribution to improving healthcare in the developing world**, GlaxoSmithKline plc, Greenford.
 2 European Federation of Pharmaceutical Industries and Associations (EFPIA) (2001) **Non-exhaustive list of initiatives carried out by the pharmaceutical industry to combat health problems in the developing world**, EFPIA, Brussels.

Health Research for Development (1990) and its successor, the Task Force on Health Research for Development (1991) that all countries should set priorities for research into healthcare. However, given that in many developing countries, most research on healthcare is externally funded, we consider that sponsors have a responsibility to consider their own research priorities in the light of national priorities which exist in host countries.

- 2.32 We do not take the view that all externally-funded research should fall within nationally defined priorities, since all research contributes to the development of local skills and expertise in research, quite apart from the inherent value in diversity of research. However, there is a careful balance to be drawn. The inherent inequalities of power and advantage between developed and developing countries require that particular care is needed to restrain any tendency on the part of the sponsor to pursue their interests to the detriment of those of the host country. **We therefore recommend that when research funded by external sponsors is proposed which falls outside the national priorities for research into healthcare set by a host country, those proposing the research be required to justify the choice of the research topic to the appropriate research ethics committees in both the host and sponsoring countries.**

Developing new interventions

- 2.33 As we have seen, socio-economic development is usually, although not always, associated with an increase in life expectancy and reductions in the many causes of morbidity. In general, improvements in healthcare can be brought about more rapidly than improvements in socio-economic status, although the two are closely linked. While it is clear that poverty is a major

determinant of ill-health, there is increasing evidence that poor health significantly impedes development.³³ Consequently, there has been a drive to find more effective medicines and vaccines for the treatment and prevention of some of the major diseases afflicting people in developing countries. The development of such interventions may have the dual effect of directly promoting improved health and leading to further health gains through the impact that such improvements will have on socio-economic development. However, some have argued that such a focus may distract attention from interventions directed at reducing socio-economic inequalities as the fundamental means of improving health.

2.34 Because budgets for health are very restricted in many developing countries, interventions that are to be widely deployed must be affordable. Ideally, they would be provided or purchased locally at low cost. Examples of such interventions include insecticide-impregnated bed-nets to protect against malaria, and vitamin A supplementation to reduce child mortality. In areas in which malaria is highly prevalent, it has been shown that the provision and use of insecticide-impregnated bed-nets, which cost less than \$10 each, reduce child mortality rates by 20% or more.³⁴ In large areas of the world where there is vitamin A deficiency, the administration of a dose of this vitamin to children every four to six months, at a cost of a few pence a dose, has also been shown to reduce total child mortality rates by around 20% (although greater costs are incurred in setting up a mechanism to ensure that children regularly receive vitamin A).

2.35 In relatively common use are some interventions that may be costly but which may be supplied at subsidised prices, or free of charge, by donor agencies or organisations from developed countries. Increasingly, international agencies have been negotiating with pharmaceutical companies to obtain concessions to supply medicines and vaccines at 'affordable' cost in developing countries through tiered pricing schemes or, in some instances, by donations of products for such use. These issues are discussed further in Chapter 9. Examples of these concessions include many vaccines and the very substantial donations of medicines that have been made by pharmaceutical companies for the treatment of river blindness (onchocerciasis) with ivermectin, elephantiasis (lymphatic filariasis) with ivermectin and albendazole, trachoma with azithromycin and malaria with Malarone®. Donor agencies have also made contraceptives widely available at little or no cost in developing countries and large numbers of condoms have been supplied in an attempt to slow the spread of HIV infection.

BOX 2.6 Burkitt's lymphoma

Burkitt's lymphoma is a childhood tumour first described in 1958. The disease is rare in Western countries but endemic to African countries such as Kenya and Uganda. Burkitt's lymphoma accounts for over half of all childhood cancers in Africa, affecting about two in 100,000 children each year. However, it is a rare cause of death when compared to diseases such as malaria (which causes to 20% of childhood deaths in the worst affected areas).

Despite its rarity, Burkitt's lymphoma was comprehensively researched in the 1950s and 60s in Africa. A team of researchers led by Burkitt charted its occurrence from Uganda to South Africa, determined the altitude-dependency of the disease, its common occurrence in malaria-endemic areas and its association with the presence of antibodies to the Epstein-Barr virus. The value of this early research to subsequent cancer research and treatment is now well recognised.¹

1 Magrath IT (1991) African Burkitt's Lymphoma. History, biology, clinical features and treatment, **American Journal of Paediatric Hematology/Oncology**, 13(2) 222–46.

33 Sachs and colleagues have argued strongly the latter point in respect of malaria and other diseases. For example, see Gallup JL and Sachs JD (2000) **The Economic Burden of Malaria**. **CID Working Paper No. 52**, John Luke Gallop, Jeffrey D Sachs and the President and Fellows of Harvard College at <http://www2.cid.harvard.edu/cidwp/052.pdf>

34 Lengeler C, Armstrong-Schellenberg J, D'Allesandro U, Binka F and Cattani J (1998) Relative versus absolute risk of dying reduction after using insecticide-treated nets for malaria control in Africa, **Tropical Medicine and International Health**, 3(4): 286–90.

- 2.36 We have noted above that for many infectious diseases affecting predominantly those in developing countries there are either no effective treatments or vaccines available, or there is a need to develop improved or new interventions. Recent advances in microbiology and biotechnology may lead to the development of new vaccines within the next decade. Not all vaccines will provide protection against the target diseases and rigorous evaluation will be needed before their use in public health programmes. Advances in biological knowledge will similarly expand the range of potential diagnostic tests and therapeutic interventions, and these will also require careful evaluation before widespread introduction and use.
- 2.37 There are, of course, substantial costs associated with bringing a new medicine or vaccine into use for public health.³⁵ In the case of most new medicines, the development costs will be borne by a pharmaceutical or biotechnology company. In the case of vaccines, global public-private partnerships such as IAVI promise to play a key role in the development of new products directed at the developing world. There are few public institutions, even in the developed countries, that are in a position to underwrite the heavy costs of developing compounds discovered in their own laboratories to the point of marketing approval. These costs and the time-scales of the development process will be reflected in the prices placed on new medicines by the companies producing them.³⁶ New medicines are priced to cover not only the costs of their own development, but also the costs of those potential treatments that fail in development. It is currently estimated that only one out of every 5,000 or so compounds discovered will reach the market place.³⁷ Of these, only a few will be major 'blockbuster' medicines which produce very high income for a company. In addition, the discovery of new medicines is based largely on the application of new technologies which requires very considerable investment in R&D. A significant proportion of the sales revenue of a major pharmaceutical company (15–18% of sales in the UK industry) is therefore ploughed back into R&D.
- 2.38 The high costs of development for new medicines means that the pharmaceutical industry has generally invested in R&D for medicines for diseases which affect large numbers of people who can afford to pay for treatment, such as heart diseases, respiratory diseases, inflammatory diseases and cancers. Through the development of successful medicines for these diseases, companies aim to recover their costs, invest in further R&D and return profits to the shareholders. Consequently, diseases which affect only small numbers of patients, or which affect large numbers of patients who have no resources in their healthcare system to buy new medicines, have tended to be ignored. The small market (in terms of purchasing power, rather than population size) cannot support the effort required to bring a medicine from the laboratory to the clinic.
- 2.39 These are the so-called 'neglected diseases' and include many of the major tropical diseases, as well as diseases which only affect small numbers of people in developed and developing countries. For example, Table 2.4 lists the limitations of the current medications available to

35 Pharmaceutical companies have estimated this cost to be in excess of \$500 million. In contrast, a recent study by Tufts Center for the Study of Drug Development put the cost of the development of a new prescription medicine at \$802 million (see Tufts Center for the Study of Drug Development press release 'Tufts Center for the Study of Drug Development Pegs Cost of a New Prescription Medicine at \$802 million at <http://www.tufts.edu/med/csdd/images/NewsRelease113001pm.pdf>). Public Citizen claimed that the figure was actually in the order of \$110 million (see Public Citizen (2001) **Rx R&D Myths: The Case Against the Drug Industry's R&D 'Scare Card'**) and that the estimate of pharmaceutical companies was unreliable as it included the cost of all failed medicines, the expense of using money for research into medicines rather than other investments and did not account for the tax reductions companies obtain for R&D. However the validity of Public Citizen's claims have been challenged and attributed to 'methodological shortcomings' (see Ernst and Young (2001) **Pharmaceutical Industry R&D Costs: Key Findings about the Public Citizen Report**).

36 However, other factors will also come into play in the determination of pricing. The longer the development time for the new product, the shorter the unexpired patent life when it reaches the market. The period of exclusive sales during which development costs can be recovered is therefore shorter.

37 Spilker BA 'The Drug Development and Approval Process', PhRMA at <http://www.phrma.org/searchcures/newmeds/devapprovprocess.phtml>. This is based on research carried out by Tufts Center for the Study of Drug Development which looked at medicines approved for the period 1993–1995 and found that only five in five thousand compounds entering preclinical testing reached testing in humans and only one in five of those tested in humans was approved for sale.

Table 2.4**Limitations of medicines for malaria**

Medicine	Year of approval or use	Limitations
Quinine	1800s	Difficulties of use and effectiveness due to long treatment regimen and safety issues (e.g. tinnitus).
Chloroquine	1947	Increasing levels of parasite resistance have developed to this treatment.
SP (Fansidar)	1969	Increasing levels of parasite resistance have developed to this treatment and there are some side effects.
Artemisinins	1970s onwards	Difficulties of use and effectiveness as a single agent related to short half-life and long treatment regimen. Primarily promoted for use in combinations with other treatments, but this generates issues of compliance. Limited manufacture to the standards of good manufacturing practice. Some outstanding safety concerns but clinical experience on the whole is positive.
Mefloquine	1985	Relatively expensive, in some areas there is parasite resistance to this treatment and there are concerns about its safety.
Halofantrine	1988	Extremely expensive, some forms of malaria are resistant to this treatment and there are serious cardiotoxicity-related concerns about its safety.
Malarone	1996	Prohibitively expensive. Efficacious but there is the potential for forms of malaria to become resistant to this medicine. There is already resistance to individual components of the combination medicine.
Co-artemether	1998	Relatively expensive. Efficacious but there is the potential for resistance to develop.

treat malaria, a disease which was estimated to cause the loss of 45 million DALYs in 1999.³⁸ In 1996, the market for antimalarials was estimated at US\$100–200 million while the market for antibacterials was over US\$16,000 million (three products had sales of over US\$800 million). While only one to two antimalarials are developed each decade, three to four new antibacterials reach the market each year. Moreover, of the antimalarials that have been developed, many cannot be afforded by patients in developing countries and are largely limited to the tourist market. Recently, however, as we have seen, there have been some promising developments in the area of public–private partnerships (see paragraph 6.27).

2.40 Pharmaceutical companies, encouraged by international agencies, are also starting to look for more economical, but effective, ways of using existing medicines to control diseases such as HIV/AIDS. For example, very recently, companies have begun to adapt their pricing structure to enable developing nations to receive medicines for HIV/AIDS at a fraction of the market price in the developed world, or at no cost, and there is increasing pressure on these companies to continue down this route. The World Trade Organisation (WTO) has recently clarified the position of its members with regard to their rights to implement the compulsory licensing of patented medicines when there is a public health emergency. Under such circumstances countries may manufacture generic³⁹ versions of patented medicines although countries without manufacturing capacity may not import these medicines.⁴⁰ However, the costs of many generic medicines will remain beyond the healthcare budgets of the majority of developing countries. In the case of antiretrovirals for

38 WHO (2000) Annex Table 4: Burden of disease in disability-adjusted life years (DALYs) by cause, sex and mortality stratum in WHO regions, estimates for 1999: 170.

39 Generic medicines are chemically the same as brand name medicines. They have the same characteristics (e.g. intended use, dosage, route of administration, safety, and quality) but are typically much lower in price than their branded counterparts.

40 World Trade Organization (2001) **Declaration on the TRIPS Agreement and Public Health (Doha Declaration)**, WT/MIN (01)/DEC/2, World Trade Organization, Geneva.

HIV/AIDS, even if the medicines were provided at no cost, the infrastructure required for delivery and monitoring side effects would be prohibitively expensive for most of the developing world.

- 2.41 The costs of evaluating a potential intervention for a tropical disease are substantial and, in general, cannot be covered by a developing country alone. For evaluation studies, pharmaceutical companies often donate products for trials and other costs involved may be met by international agencies. However, once efficacy has been established, the long-term supply of a product for public health use in a developing country may be very problematic if, as is often the case, the cost is beyond the resources available in the healthcare system. The slow deployment of vaccines against hepatitis B in developing countries and the restricted use of praziquantel against schistosomiasis are such examples.
- 2.42 However the cost of an intervention at the time of evaluation may fall substantially in due course (see Box 1.3). There have also been examples where beneficial interventions that are relatively costly can be used to argue the case for lowering, or subsidising, the price for developing countries. For example, in The Gambia, the demonstration of a strong protective effect of a vaccine against disease due to *Haemophilus influenzae* type b (HIB), has been an important factor in the more widespread promotion and subsidy of this vaccine, despite its substantial cost.
- 2.43 Not all 'new' interventions are expensive, however, and perhaps some of the most important advances have been made using products that are within, or close to, the resources that might reasonably be made available locally. For example, oral rehydration solution is cheap to produce and is highly effective at reducing mortality from diarrhoeal diseases.

The future

- 2.44 It can be expected that in the future there will need to be a radical change in the approach of the pharmaceutical industry to its R&D programmes and its investment in research. The first phase of the human genome project is now largely completed and it is reasonable to expect that increasing numbers of genes associated with, or perhaps causing, human diseases will be identified. This will provide research scientists with potential new molecular targets for the discovery of new medicines over the longer term. This approach has the potential to provide cures where existing medicines have only been able to alleviate the symptoms of a disease. However, many diseases will have multigene substrates, and selecting the optimal molecular target will be a substantial challenge.
- 2.45 However, it is possible that some of the currently 'common' human diseases will in fact be found to be a collection of different diseases, sharing a common appearance, but caused by different molecular mechanisms. Several common diseases may become collections of conditions affecting much smaller populations. Each condition may require a specific treatment. However, the cost of discovery, development and registration of new medicines for each condition may change, for example as clinical trials may change in size and complexity. It follows that for some diseases or sub-sets of disease improved treatments may only be available at higher prices. Providers of healthcare in the developing and developed world will need to adapt to the new approach. They will need not only to consider the cost of the medicines but also to take account of the cost-effectiveness and outcomes of new interventions, for instance reduced hospitalisation within the overall healthcare delivery system, as well as the more general economic benefits. In developing countries these new approaches will be difficult to implement, indeed, existing infrastructure is challenged to deliver current diagnostics and medicines. For the providers of healthcare, the provision of the infrastructure required to employ 'gene-based' or pharmacogenetic⁴¹ medicines

41 Pharmacogenetics is the study of how genetic differences influence the variability in patients' responses to medicines.

effectively, i.e. screening and diagnostics, will present yet further challenges. For those wishing to carry out clinical trials, the costs may well become prohibitive if they must provide the necessary infrastructure to undertake such research. For these reasons, the pharmacogenetic approach to the development of medicines is unlikely to be available for developing countries for the foreseeable future.

36 หน้าว่าง



Chapter 3

*Social and
cultural issues*

38 หน้าว่าง



Introduction

- 3.1 Developing countries are not a homogeneous group. They differ in many ways: culture, history, size of population and rate of growth, gross national product (GNP) per capita and levels of education (especially of girls and women). As discussed in the previous chapter developing countries also vary in terms of the technological and other forms of infrastructure they have in place, in their spectrum of health problems and in the quality and availability of healthcare. There are differences in the degree of social and economic inequality within countries. The degree of freedom of expression, recognition of human rights and extent of social harmony or disharmony are also highly variable. Rapid social and cultural changes are occurring in some developing countries following increased interactions with external cultures and technologies. As a consequence of all of these factors, it is inappropriate to regard developing countries as a single entity and their diversity must be taken into account when issues arising from research related to healthcare are under consideration. In addition, there are significant variations within developing countries, especially those countries with a number of ethnic groups and significant differences in socio-economic status.
- 3.2 This chapter discusses the social and cultural contexts in which research in developing countries is conducted, providing a background to the discussion in the following section of the Report. It also highlights issues to which external sponsors and researchers should pay particular attention when research in developing countries is proposed. The interpretation of universal ethical principles in the light of social and cultural contexts is discussed in Chapter 4, while the implications of such contexts for the consent process are discussed in more detail in Chapter 6. While traditional systems of medicine are discussed in this chapter, the purpose of the discussion is to illustrate the contexts within which prospective participants may make decisions, rather than evaluating the effectiveness and evidence base underlying such systems.

Prevalence of alternative medical systems

- 3.3 One factor that may influence prospective participants in research is their understanding and use of traditional methods of healthcare and medical treatment, as well as the nature and level of their familiarity with evidence-based modern healthcare and research related to healthcare. There are a mix of modern medical and indigenous healthcare facilities in developing countries. For example, in the Middle East, parts of Africa, and South and South-East Asia versions of the Yunani system exist (derived from classical Arabo-Greek Galenic medicine) alongside modern healthcare and folk healing, as do the Ayurvedic system in India and the various Chinese therapeutic systems. This co-existence of different systems is also a feature of developed countries, as people increasingly seek complementary and alternative therapies, in addition to modern healthcare.
- 3.4 While there is much variation between continents and between regions within continents, local populations sometimes identify modern healthcare as especially valuable for acute conditions (following the successful use of antibiotics for eliminating infections rapidly). In contrast, long-term recurring problems may be ascribed to social, emotional, cosmic or religious causes, for which practitioners of alternative therapies are sought. This sometimes entails patients making choices along established lines: the first visit being to alternative medical practitioners or healers and subsequent ones to modern healthcare practitioners, or vice versa. This is a form of decision-making that may be unwelcome to researchers in both host and sponsoring countries. It is, however, a reality that in the long term it is more efficient to address than ignore.

BOX 3.1 Combining medical research and traditional healthcare

Ghana

Although there are effective medicines to treat malaria, many children in rural Africa who develop severe malaria die before they can receive help. In some such regions, the severe form of the disease (cerebral malaria which causes convulsions) is thought to be caused by evil spirits. As a result, children who have severe malaria with convulsions are often sent to traditional healers. It is also sometimes believed that such children should not receive injections, although they cannot take medications orally. A new medicine (administered as a rectal suppository) that could treat such cases of malaria is being tested in a district in northern Ghana.¹ This is part of a multi-country study sponsored by WHO in Ghana, Nigeria, Tanzania and Bangladesh. The study team in Ghana is working very closely with over 400 traditional healers to identify cases of severe malaria, provide the new medicine, and refer these cases to the nearest health facility for treatment. In all these cases the traditional healers' role is recognised and the credit for the survival of the children jointly acknowledged.²

Burkina Faso

In Burkina Faso a current research programme combines modern healthcare and African traditional medicine in providing treatment for people living with AIDS. Practitioners of modern healthcare are working with traditional health practitioners to assess the effects of traditional healthcare practices on patients. In one example of effective integration of traditional medicine into a modern health system, a team composed of scientists, Health Ministry officials, members of the Burkinabe Association of Traditional Health Practitioners and others, developed a protocol for the management of patients.³

1 The research is designed to determine the benefit of early treatment with rectal artesunate capsules.
 2 The double-blind randomized clinical trial of artesunate rectal capsules on child survival in the Kassena-Nankana district Ghana, is funded by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Disease (TDR).
 3 The Health Minister's meeting 'Integrating Traditional Medicine into Health Systems: the example of Burkina Faso' was held in Ouagadougou, Burkina Faso, from 28 August to 2 September 2000.

Combining modern healthcare and traditional medicine

3.5 Most healthcare-related research that has been externally sponsored in developing countries has not taken account of traditional medicine. In some circumstances, the belief systems of traditional healers and biomedical researchers may be so incompatible that the two groups will be unwilling or unable to collaborate in research. In other cases such collaboration is desirable, or even essential, for research to be successful. Two such examples involving malaria and HIV/AIDS are set out in Box 3.1.

Concepts of illness, disease, misfortune and death

3.6 In developing countries, sickness may become merged with general ideas of misfortune. For example, one villager may be physically sick, another emotionally distraught or suffering from a mental illness and yet another's herd of livestock may have died. All three may be regarded as suffering from the same generalised affliction, which may be diagnosed by a shaman as someone else's witchcraft or bad spirits.¹ The first two villagers' conditions may be treated by modern healthcare practitioners and indigenous herbalists as physical ailments.²

3.7 It is commonplace in Africa for certain ailments, especially those affecting children, to be ascribed to the effects of spirits or violations of prohibitions. Researchers may wish to avoid taking account of such explanations. Yet, these

1 A shaman is someone who is believed to mediate between the spirit world and humanity, and is able to enter into a trance or similar state and then diagnose and prescribe or effect cures for disease. The term was originally coined by scholars who were studying societies in Siberia and central Asia, and was later extended to similar religious complexes found elsewhere in the world.
 2 Littlewood R (1988) From vice to madness: the semantics of naturalistic and personalistic understandings in Trinidad local medicine. **Social Science and Medicine**, 27(2) 129-48.

indigenous explanations have a kind of reality as an explanatory system of ill-health and need not be incompatible with the research. Thus, while malaria or diarrhoea are indeed often ascribed to affliction by spirits, they can also be treated as a biomedical condition.

- 3.8 Local people will usually accept both types of explanation as contributing to an understanding of malaria. Spirits may be invoked to explain recurrent illness (for which the traditional remedy is expulsion of the spirits causing the illness). Bad water or an infestation of mosquito larvae can be understood as explaining the immediate symptoms (with such remedies as the development and use of clean water, chemically protective mosquito nets and medicines, or clearing away undergrowth and stagnant pools around a homestead). Such conflict of ideas and explanations is structural and broadly unavoidable, and should be acknowledged and dealt with by researchers on a day-to-day basis.
- 3.9 Differences from Western beliefs are sufficiently widespread to affect the views of local participants in research and to influence the conduct and progress of research related to healthcare. Local researchers, even if trained in modern healthcare, are likely to be accustomed to the concepts and practices following from traditional health practices and may view them as useful. Although it is in practice difficult to assess the efficacy of such systems, biomedical researchers may wish, provisionally at least, to keep in mind a distinction between local practices which are beneficial and worth encouraging (such as passing a knife through a flame to sterilise it before cutting a newborn's umbilical cord), and those which are harmful (such as applying animal dung to the stump of the umbilical cord) and should be discouraged.³ The use of other kinds of treatment where there is no evidence base for the assessment of useful or ill-effects may be best left to the judgement of local individuals, families and practitioners, and in some cases may be worthy of research to establish effectiveness.
- 3.10 Participants' beliefs about common techniques used in research, such as taking blood and urine samples, or giving injections, will also have an impact on the conduct of research. For example, sensitivity to the taking of blood samples is widespread in many parts of Africa (see Box 3.2). Some potential participants in research believe that researchers sell blood. Such individuals may resent the exercise while others may agree to provide just a very small blood sample. This might encourage researchers and field assistants to use deceptive methods to obtain larger amounts of blood if this is required by the study protocol. Providing urine samples is less unpopular and where such samples are a possible alternative to blood samples, may be preferred by study participants. There is often greater reluctance to provide samples of faeces. In part this may be because of the messy procedures for sample collection, especially as water-based sanitary facilities are often not available and the only alternative is a pit latrine. There is, however, also the belief in some areas that faeces may be used for witchcraft. In contrast to reservations about giving samples, in many developing countries injections are very popular.⁴ If

BOX 3.2 Blood samples in Malawi

In Malawi there is a widespread belief that a person's blood contains his or her spirit. If blood is taken in any quantity it is feared that the spirit is also lost. Whoever takes blood is believed to control the spirit and body of the individual from whom the blood was taken. This belief does not prevent the taking of blood samples within health facilities when the individual is presumed to be sick. However, population-based studies which require blood samples are extremely difficult or impossible to conduct unless the participants are brought to a healthcare unit. As a result, taking blood samples is minimised in community-based research studies.

3 World Health Organization (1998) **Care of the umbilical cord: a review the evidence 1998 - WHO/RHTMSM/98.4**, World Health Organization, Geneva.

4 See Reeler AV (2000) Anthropological perspectives on injections: a review, **Bulletin of the World Health Organization**, 78(1) 135-43.

such belief systems are to be taken into account when research is designed, researchers will require knowledge of, or access to those with knowledge of, the languages and concepts used in discussions and practices of healthcare.

The doctor–patient relationship; the healer–client relationship

- 3.11 It cannot be assumed that there is only one model of doctor–patient or healer–client relationship. This applies not just across the spectrum of medical systems but also within healthcare systems. An early Western model of the doctor–patient relationship saw it as essentially harmonious and based on the patient’s unquestioning acceptance of the doctor’s superior status and skills.⁵ A later model proposed an inherent conflict between doctor and patient deriving from the difference in power between the two, a difference which in some cases has to be negotiated and which may therefore not be harmonious.⁶
- 3.12 A similar range of possible doctor–patient relationships is likely to be found in different cultures. One report from Pakistan refers to traditional Muslim healers (called *pir*) who are regarded as imbued with God’s power and so never need to make diagnoses: just seeing the patient will allow them to know the patient’s condition and prognosis.⁷ Reports from Africa suggest much more negotiability between doctor and patient, with the latter entitled to argue with the doctor or healer over the diagnosis and possible cure.⁸ In between are the more complicated variations, for example in which healers physically identify or empathise with patients, by co-ordinating their pulse rates with those of the patient and then using this common point of identification for diagnosis and cure.⁹
- 3.13 Researchers from developed countries may not be fully aware of prospective participants’ considerable trust in and respect for medical doctors and other healthcare practitioners, even those with modest qualifications. This may be especially true if the healthcare practitioners have been trained in Western countries. It is questionable whether researchers from developed countries are well prepared for the enormous responsibility that this attitude of respect and trust places upon them. The implications of this attitude for the consent process are discussed in paragraph 6.24.
- 3.14 In many instances researchers from developed and developing countries may have more in common with their counterparts from other countries than they do with the population under study in rural or less-educated areas. Discussion with interpreters, cultural assistants, indigenous healers and shamans will provide researchers with a means of understanding some of the religious and cultural issues that may have a bearing on research related to healthcare. Such cultural understandings are especially important if the researchers are principally male and the interpreters and cultural assistants are predominantly female. Similarly, gender differences among local practitioners may be significant: for instance, in some societies, traditional herbalists

5 Parsons T (1964) **Social structure and personality**, Free Press of Glencoe, New York; Collier-Macmillan, London.

6 Hahn RA and Gaines AD (eds) (1985) **Physicians of Western medicine: anthropological approaches to theory and practice**, Reidel, Dordrecht. Kleinman AK (ed) (1980) **Patients and healers in the context of culture. An exploration of the border-land between anthropology, medicine and psychiatry**, University of California Press, Berkeley.

7 Ewing KP (1984) The Sufi as saint, curer and exorcist in modern Pakistan. In Daniel EV and Puggy JF (eds) **Contributions to Asian Studies**, EJ Brill, Leiden, Netherlands.

8 Davis-Roberts C (1981) Kutambuwa ugonjuwa: concepts of illness and transformation among the Tabwa of Zaire, **Social Science and Medicine**, 15(3) 309–16.

9 Daniel EV (1991) The pulse as icon in Siddha medicine. In Howes D (ed). The varieties of sensory experience, **A Sourcebook in the Anthropology of the Senses**, University of Toronto Press, Toronto. Hsu E (2000) Towards a science of touch, Part I: Chinese pulse diagnostics in early modern Europe, **Anthropology and Medicine**, 7(2) 251–68. Hsu E (2000) Towards a science of touch, part II: representations of the tactile experience of the seven Chinese pulses indicating danger of death in early modern Europe, **Anthropology and Medicine**, 7(3) 319–33.

are male and shamans female. Differences in interpretation as a result of gender may need to be taken into account in planning local participation in research and understanding of research as carried out in developed countries.

- 3.15 In addition, there may be a tension between participants' respect for those with training in developed countries, education and knowledge and their respect for traditional figures of wisdom and authority, including leaders of the community. Elders in the community commonly occupy positions of trust and may be respected for their local knowledge: differing circumstances of particular situations may determine which kind of knowledge is preferred, and by whom. For example, differing views as to where pregnant woman should have their confinements were observed in rural coastal Kenya before the advent of AIDS. Some of the older men preferred pregnant women to have their confinements at home attended to by a traditional midwife.¹⁰ A number of them thought hospital confinements were an unnecessary expense, as they considered the traditional method to be successful. In contrast, almost all the pregnant women wanted to give birth at a local mission hospital, with family members in attendance.¹¹ However pregnant women also often turned to older members of the homestead for healing and dietary advice.

Informing prospective participants about research

- 3.16 In many developing countries, concepts of respect for the family and community are equally as important as, or more important than, concepts of individual autonomy and rights. The belief that there may be mutual effects on each other by members of a kinship or other group is found in many non-Western societies. For example, in parts of Africa, if one person commits an offence, such as the violation of a sexual prohibition, the whole village or family may have to undergo a cleansing ritual in order to rid themselves of the harmful effects of that person's act.¹² This is a quite different understanding of individual autonomy from that found in many developed countries. In such circumstances, to seek individual consent without first creating public or group acceptance is likely to cause conflict within a community.
- 3.17 Often public discussion, followed by consultation with family units including women members, appears the most feasible and productive course to inform prospective participants about research, although variations in the cultural context will shape the manner in which this can be done. Without doubt it is often a slow process, requiring knowledge not only of the local political structure, language and relevant idioms but also of the customs defining behavioural etiquette and local moral systems (see Box 3.3). Community discussion and acceptance are also perceived as valuable and integral parts of promoting respect for persons and the dignity of individuals in developed countries.

Decisions about research

- 3.18 In some districts of developing countries, decisions about an appropriate course of action are made within a hierarchy of customary roles in the family and community. Men are most often in

¹⁰ Parkin D (2001) Personal communication, University of Oxford.

¹¹ This preference appeared to be based on two factors: young women's claims, based on observation, that hospital births were more successful than homestead ones; and a wish to avoid the traditional midwife's method of inducing slow birth by forcing the infant out through externally-applied pressure.

¹² See, for example Turner VW (1968) **The Drums of Affliction: a study of religious processes among the Ndembu of Zambia**, Oxford University Press, Oxford.

BOX 3.3 Discussing research: China

Government policy in mainland China has imposed a degree of uniformity in the structure of rural villages, where public discussion is the most likely forum in which the objectives of research can be communicated to members of a village. Villages below the level of townships tend to be self-governing collective units, organised by elected village cadres, some of whom are government party members. It is, for instance, through these cadres that information and monitoring with regard to the one-child family policy is carried out. Although imperfect, there is thus in principle a well-established official medium for the public discussion of research related to healthcare, its objectives and the need for local participants. Provided that the cadres in China accept the value and feasibility of a research project, would-be participants can choose whether or not to consent to participate in research. Moreover, with the possible exception of some remote areas, it is unlikely in modern China that women are expected to obtain the permission of men or elders before agreeing to be involved in research. Nevertheless, before consent can be sought, a visiting research team's proposals will need to be discussed in an open manner through the offices of the village cadre committees.¹

1 Pieke F (1996) **The Ordinary and the Extraordinary: an anthropological study of Chinese reform and the 1989 People's Movement in Beijing**, Kegan Paul International, London and New York. Hsu E (1999) **The Transmission of Chinese Medicine**, Cambridge University Press, Cambridge.

charge of such decision-making about participation in research by virtue of their status as head of the household or community (see Box 3.4). In addition mothers-in-law commonly exert power over daughters-in-law in some South Asian regions. Women, particularly young women, may not therefore always be able to express personal opinions on even minor matters, let alone the issue of whether they would like to take part in research. The notion that individuals are free to make their own decisions will therefore be less familiar to such women. The role of researchers in such circumstances is discussed in Chapter 6. Given that mortality and morbidity in both children and women are unacceptably high in many developing countries, research relating to child and reproductive health remains a priority. In a social context where women and children are vulnerable, they may be excluded from participating in research that is likely to benefit them or, conversely, exploited for research purposes precisely because they are vulnerable.

3.19 Attitudes have changed dramatically in much of Africa, where many women, especially in non-Muslim societies, have now cultivated a more assertive position with regard to healthcare, often aided by mission hospitals, clinics and health-focused non-governmental organisations (NGOs) (see Box 3.5). The rapid and increasing emergence of households

BOX 3.4 Consent to research: Uganda

In some areas of Uganda that hold to traditional social and cultural values, the head of the immediate family is a man (husband/father) and it is widely recognised and expected that he takes the final decision on all matters, especially sensitive ones affecting family members. In these areas, family members who do not submit to such decisions may face serious consequences including domestic violence and/or divorce. Thus, in such circumstances women and children will tend not to participate in a study unless permission has been granted by the head of the household. However the Ugandan guidelines require investigators to obtain 'the legally effective informed consent of the individual research participant'. In addition they explicitly state that 'a community leader may not consent to the participation of community members'.¹

1 National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference) (1997) **Guidelines for the Conduct of Health Research involving Human Subjects in Uganda**, National Consensus Conference, Kampala, Uganda: 32.

headed by women in parts of Africa as a result of AIDS may have accelerated these changes in attitude. As cultures are not fixed, researchers may need to find means of fostering discussion about what is required by cultural norms in a particular context. For example, research in South Africa has shown that even within a culture with strong beliefs about the importance of the community, many women favour the approach of requiring individual consent to research.¹³ The issue of cultural sensitivity is discussed further in Chapters 4 and 6.

3.20 In contrast to the examples above, in Latin America, substitute consent, community consent or other types of group or corporate consent are usually not practised. Although collective information can be given to rural communities or ethnic minorities, such as indigenous populations, consent by individual participants has been the rule. In research into vaccines in Colombia involving the military population, consent was initially sought at the command level and then at the individual level, before participants were enrolled. Although the trial was fully supported by the military command, a large proportion of volunteers felt able to choose to withdraw from the vaccination scheme before the second and third doses due to a range of side-effects.¹⁴

3.21 As in developed countries, in developing countries there may be a variety of reasons why people are willing to participate in research projects. Participants may be motivated by self-interest, in particular by the belief that a research project may provide them with a new and effective treatment for their illness. Alternatively, participants may consent to take part in research because it provides their only opportunity to receive adequate healthcare. In the case of HIV-positive participants in research in Thailand, a primary motivation to participate was the provision of an effective treatment for their condition (see Box 6.5). Participants may also be motivated by altruistic beliefs about the power of the research to benefit their community, whether that community is defined in geographical terms, or in terms of the community of people with a particular disease. Research in Chile has shown that, for some women, participation in research was a valued opportunity to 'contribute to all women's health', or 'to a better future'.¹⁵

BOX 3.5 Consent to research: Ghana

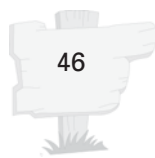
In a study in northern Ghana to determine culturally appropriate models of health and family planning services for the population, a district-wide experiment was established to document the impact of health and family services on child mortality and fertility.¹ The community participated actively in the development of the experiment and approved its design. A key feature of the research was the provision of modern family planning services to men and women in this rural population, where they had previously not been available. The men insisted on being consulted before their wives were offered family planning services. However, the women, with the assistance of the research team, organised several community meetings to discuss the implications of consent in the male-dominated society. After several public meetings where the issue was openly debated between the men and women, the women succeeded in convincing the men to accept that the women could use the family planning services either with dual consent of the couple or with the consent of the woman alone. The research team also agreed that information on consent would be treated as confidential.

1 Binka FN, Nazzar A and Phillips JF (1995) The Navrongo community health and family planning project, *Studies in Family Planning*, 26(3) 121-39; Nazzar A, Adongo PB, Binka FN, Phillips JF and Debpuur C (1995) Developing a culturally appropriate family planning program for the Navrongo Experiment, *Studies in Family Planning*, 26(6) 307-324.

13 Lindegger G (2002) Culture and informed consent in clinical trials in South Africa, Third Global Forum on Bioethics in Research, Capetown, South Africa, 21-23 February 2002.
 14 Velez ID, del Pilar Agudelo S, Arbelaez MP, Gilchrist K, Robledo SM, Puerta JA *et al* (2000) Safety and immunogenicity of a killed *Leishmania* (L.) amazonensis vaccine against cutaneous leishmaniasis in Colombia: a randomized controlled trial, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 94(6) 698-703.
 15 Sanchez S, Salazar G, Tijero M and Diaz S (2001) Informed consent procedures: responsibilities of researchers in developing countries, *Bioethics*, 15(S16) 398-412.

3.22 Prospective participants in developing countries place high value on healthcare. Consequently it is often assumed that they may be more likely to participate in research related to healthcare, although this is not easy to demonstrate. In addition, a lack of familiarity with the methods and rationale of research related to healthcare, may lead participants to believe that the primary purpose of research is to provide them with therapy, rather than to obtain information (commonly called 'therapeutic misconception'). The US National Bioethics Advisory Committee (NBAC) recommended that investigators working overseas must indicate in their research protocols how they intend to minimise the possibility of therapeutic misconception.¹⁶ We conclude that investigators conducting studies in developing communities have a special responsibility to explain to those participating in research that the research may not benefit them as individuals so that they do not participate in the false expectation of gaining a direct benefit. In areas where physicians are thought of solely as healthcare providers, and where research is a novel concept, particular care must be taken. Issues relating to consent are discussed in more detail in Chapter 6.

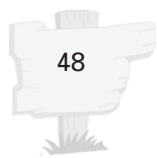
16 National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries**: Recommendation 3.10.



Chapter 4

The ethical framework

48 หน้าว่าง



Introduction

- 4.1 In Chapter 2 we noted the wide variations in the health of populations around the world. These variations exist in a context of considerable interdependence between countries, not least with regard to international trade. Scientific research and research related to healthcare are themselves international enterprises, the findings of which may transcend national and political borders. Commercial enterprises, including pharmaceutical companies, seek to take legitimate advantage of the economies of scale that global markets offer. The economies, social systems and politics of countries are thus bound together in complex ways.
- 4.2 As well as considerable variations in health of populations, there are also wide variations in the ability of different countries to cope with the problems which they confront. These differences of capacity stem largely from varying economic resources, but also relate to variations in administrative and political capacity and the differential development of expertise in scientific and technical disciplines in the world. Moreover, as discussed in Chapter 2, it is often the case that those countries with the greatest health needs are also those with the least capacity to deal with them. For example, some of the highest rates of HIV infection are in countries that are among the poorest of the world. In situations of poverty, with very limited scientific, administrative and political capacity, as well as economic inequalities, individuals and organisations face major difficulties in delivering the healthcare needed.
- 4.3 Many interpretations can be, and have been, offered for this pattern of global inequality. One view is that it is a legacy of colonialism and empire. Built upon a basis of economic exploitation, newly de-colonised nations in the middle of the twentieth century were left with inadequate political and social institutions with which to face the challenges of economic and social development. Another view is that the pattern of global inequality represents a series of structural barriers raised against the poor, making it extremely difficult, if not impossible, for them to develop an economic basis sufficient to sustain a reasonable standard of life for their citizens. A third view is that, despite the history of colonialism, the modern international order does offer opportunities for economic growth, provided that poorer countries have the appropriate policies and institutions in place to take advantage of their comparatively low costs to compete against established economic powers.
- 4.4 In this Report, we do not take a position on these competing interpretations. We simply acknowledge the difficulties confronting those seeking to improve the health of populations in developing societies, and we accept that the barriers to sustainable development are considerable. Yet within these constraints, individuals and corporate bodies still have choices. The moral burden of choice weighs especially heavily on those who enjoy a privileged position in the world order because, by definition, they have the greatest capacity to effect change, but it also applies more widely. In particular, the problem is raised of how to devise an approach to research related to healthcare that is consistent with the requirements of an ethical framework for research.
- 4.5 What do we mean when we speak about an ethical framework for research? We have in mind a set of principles that allow us to evaluate the actions and policies of individuals and bodies such as companies, non-governmental organisations (NGOs), international organisations or government agencies. These principles seek to identify the considerations that should apply to individuals and agencies when they make decisions or adopt policies. They constitute a framework for articulating the duties, obligations, claims and expectations of those involved in research related to healthcare.
- 4.6 We do not present these principles as part of a more general ethical theory. This does not mean that the principles are drawn from nowhere: they are widely discussed in works on ethics and

political theory. We offer them as the basic considerations which anyone concerned to reflect upon and evaluate research related to healthcare in developing countries should take into account. We consider four principles in particular:

- (i) the duty to alleviate suffering
- (ii) the duty to show respect for persons
- (iii) the duty to be sensitive to cultural differences and
- (iv) the duty not to exploit the vulnerable.

The task of the Working Party was to consider how these principles should be understood in the context of research related to healthcare in developing countries and of the particular dilemmas that arise, while taking account of the practical, social, cultural and economic circumstances that are relevant to research.

The duty to alleviate suffering

- 4.7 Medical practice is fundamentally justified by the duty to alleviate suffering. This duty has long been acknowledged in moral codes and its application to medicine is enshrined in the Hippocratic Oath. It is commonly argued, and recognised in most political structures, that the needs of one's own communities should have first claim on this duty and thus on the resources available. But this does not mean that we have no duty to contribute to the alleviation of suffering elsewhere, especially among the citizens of poor countries.
- 4.8 Since medical research, and research related to healthcare generally, make an essential contribution to the alleviation of suffering, the conduct of research which deals with the health problems in developing countries is not just legitimate, it is a moral duty. For most people, the duty to conduct research addressed to the needs of developing countries is discharged only indirectly, by government support for publicly-funded institutions such as the Medical Research Council (MRC) in the UK and the National Institutes for Health (NIH) in the US, the Framework Programmes of the European Union and the many national aid agencies in developed countries (see Box 2.2). Nonetheless, it matters morally to all of us that effective medical research and research related to healthcare is indeed carried out. There is an inescapable moral duty which must be the basis for public policy in this area.¹
- 4.9 The duty to alleviate suffering enjoins us to do what we can to reduce the amount of suffering in the world. Thus we fail to act in accordance with this duty by doing nothing to help eliminate avoidable suffering; and the more suffering we help to eliminate, the better our action. But there are many other claims on our time and resources, and acknowledging the fundamental status of the duty to alleviate suffering does not mean that it always overrides all other claims. Instead, there is a difficult task for individuals and, especially, governments to strike an acceptable balance between competing demands. It is not part of this Report to propose a method for undertaking this task. But the fact that externally-sponsored research related to healthcare may be undertaken in a context in which resources are limited has important implications for its conduct. This is one aspect of the issues about standards of care discussed in Chapter 7.

¹ Furthermore, this research is increasingly also a matter of enlightened self-interest, since immigrants from developing countries, and travellers to them, may bring some of the health problems of the developing world back to the developed world.

Respect for persons

- 4.10 The duty to alleviate suffering focuses on just one human quality, the capacity for suffering. But humans share many characteristics. As well as having common basic needs they also have the capacity to think, reason, use language and live in complex relationships with one another, thereby creating their own cultures and allowing individuals the opportunity to pursue their own projects within these cultures. This capacity for creating a life of our own is both an essential feature of common humanity and yet also something that marks out each of us as a unique source of value. It justifies the requirement that we regard each other as worthy of respect.
- 4.11 In holding every person worthy of respect, we commit ourselves to taking their interests into account when considering what to do. We may not use them as a mere means either to our own ends or to the welfare of others, and, on the presumption that they are the best guardians of their own interests, they should be involved in decisions which affect them. Hence, among other things we should not increase their risk of illness or death, misinform them, violate the integrity of their intimate relationships, or treat with indifference what they deeply value. Positively, we should support their sense of self-respect and self-worth, encourage them to develop and express their capacities, and help create conditions in which they can lead worthy and meaningful lives.
- 4.12 Understood in this way, the duty of respect for persons places important constraints on the implementation of the duty to alleviate suffering. That duty, by itself, may lead to the assumption that the less suffering there is, the better. However, the principle of respect enjoins us to consider carefully the ways in which we seek to alleviate suffering. For example, policies which violate other interests of those involved, even if they offer the most straightforward way of reducing suffering, are to be weighed carefully. Equally, issues related to balancing the interests of participants in research with the interests of the wider population who could benefit from the research results are addressed in Chapter 7.

Sensitivity to cultural differences

- 4.13 An important characteristic of externally-sponsored research carried out in developing countries is that there are often cultural differences between those organising or funding the research and the research workers and participants in the host country (see Chapter 3). The moral significance of these differences requires special attention.
- 4.14 Individuals live within particular societies, the cultural assumptions and practices of which shape their understanding of themselves and others. The ways in which different peoples define themselves in terms of gender, family, kinship, status and nation, and go on to organise relationships involving matters of authority and questions of sickness and health, are endlessly varied. Even when they are in revolt against their cultural upbringing, individuals often tend to think of themselves in the light of the concepts and understandings they have acquired in their society, including their understanding of sickness and health.
- 4.15 As a result, the general duty of respect implies a duty to be sensitive to other cultures. Thus one potential misuse of power is to be insensitive to the cultural perspectives that individuals bring to questions of health and healthcare. Indeed, the variety of beliefs and practices that exist may challenge the notions of overarching ethical principles. This in turn prompts an analysis of the relationship between the requirement of sensitivity to cultural differences and the concept of moral relativism, the view that different moral codes cannot be critically compared and evaluated.
- 4.16 In our view, recognition of the existence of diverse cultures and communities with different moral codes does not lead to moral relativism. The relativist position mistakenly suggests that because

a particular set of moral norms is embedded in the culture, it must be accepted uncritically. This is to confuse two distinct questions:

- (i) What does the local culture prescribe?
- (ii) What is the right thing to do bearing in mind the local culture?

Ethical judgements are of this second type. Thus, sensitivity to the values inherent in local practices does not require uncritical acceptance of them.

- 4.17 What then are the demands placed on us by the requirement of sensitivity to cultural differences? Plainly, one demand is the willingness to explore such differences without prejudice and to seek as far as possible to understand them informed by knowledge of local traditions and material circumstances. Equally, once this understanding has been achieved, those organising research related to healthcare should as far as possible take account of the local culture, taking the trouble to find ways that respect local practices even where, on the face of it, they complicate the research. But, it does not require those involved to compromise fundamental values. In particular, since sensitivity to cultural differences is an implication of the fundamental principle of respect for persons, if local cultures transgress values inherent in this principle, researchers will need to follow different procedures from those prescribed in the local culture.
- 4.18 This analysis is particularly relevant when we consider the need for consent by participants in clinical trials. One of the distinguishing characteristics of cultures in developing societies is that they are often less individualistic than those in Western Europe and North America. In such cultures, consent may not be seen to be a purely individual matter. It may be associated with wider obligations to family, village or clan (see paragraph 3.18). Our approach in this chapter suggests that when we come to consider the requirements for consent in Chapter 6, we need to be sensitive both to local cultural traditions and to the general requirement of respect for persons implied by our common humanity.

The duty not to exploit the vulnerable

- 4.19 We have already stressed that the context of our Report is one in which there are considerable inequalities of power and advantage between developed and developing countries. We suggest that, as a matter of moral principle, the more powerful have a duty to refrain from exploiting to their own advantage the vulnerability of the weaker. Since those with power may always be tempted to misuse it, perhaps even for what they perceive as benevolent reasons, it is important to insist on this principle.² We have a number of points to make about the principle.
- 4.20 First, it can be regarded as a further implication of the principle of respect for persons, for in exploiting others we fail to give proper weight to their interests. Secondly, like the requirement of sensitivity to cultural differences, the duty not to exploit the vulnerable merits special attention in the context of developing countries, not least because outsiders and local citizens may well differ on just what counts as exploiting or taking advantage of the weakness of others. Thirdly, it is important that the duty not to exploit the vulnerable be observed uniformly by all individuals and organisations involved in research, to avoid unfairness and the danger of undermining the principle in practice. If only some sponsors act in accordance with the principle of non-exploitation, then such scrupulous sponsors would be disadvantaged in relation to unscrupulous sponsors. Fourthly, although the duty not to exploit the vulnerabilities of others falls on all, the

² For a general discussion of the importance of protecting the vulnerable as a matter of social responsibility, see Goodin RE (1985) **Protecting the Vulnerable**, University of Chicago Press, Chicago.

nature of the obligation may change depending on who is involved. For example, those occupying positions as policy-makers in political and social organisations at national or international levels have an obligation not simply to provide for the avoidance of exploitation within the framework of existing practices and institutions, but also to pursue change in the functioning of those institutions and practices so as systematically to reduce the opportunities for exploitation.

- 4.21 Hence, the principle of not exploiting the vulnerable does not mean that we simply take the current context of research related to healthcare in the developing world as unchallengeable and unalterable. Just as it is unacceptable that local political and economic elites should seek to pursue their own goals at the expense of populations participating in research, it is unacceptable that researchers should select populations which are economically or politically weak, and therefore vulnerable to exploitation, in order to test therapies more cheaply in order to benefit other, wealthier communities. The wider roles and obligations of all those involved in research, pharmaceutical companies, international organisations, governments, and individuals in reducing global health inequities must always be borne in mind. In particular, in the context of research, researchers have a duty to enable the participant communities in developing countries to benefit, where possible, from the research conducted on them. This point, along with the broader question of developing expertise in research, is a matter to which we return in Chapter 9.

From principle to practice

- 4.22 We have discussed four interrelated ethical principles relevant to the conduct of research in developing countries. They should not be thought of as rules to be applied mechanically. By their very nature, they call for interpretation and consequently for the exercise of judgement, especially in relation to the latter two principles concerning sensitivity to cultural differences and the avoidance of exploitation. The importance of some cultural difference may not be clear initially, nor may it be clear at what point the standard of care extended to participants in research becomes exploitative. Thus, when considering how research related to healthcare should be conducted, it is important to analyse how such judgements are to be made, appraised and implemented. Principles must be translated into practice, and for this a proper procedure must exist. The analysis of such procedures is an important part of our discussion. There need to be suitably informed and accountable bodies in both the country in which the research is sponsored and the country in which it is carried out to take responsibility for striking a proper balance between the various conflicting considerations which arise. In Chapter 8 we discuss the way in which research ethics committees can play this role.
- 4.23 We emphasise one point here: the establishment and maintenance of research ethics committees is just as much an essential ingredient in the proper conduct of research related to healthcare as the functioning of political institutions is essential to the proper conduct of government. An ethical analysis does not concern itself only with identifying and setting out appropriate general values and principles. It also has to concern itself with the institutions and procedures through which these principles are put into practice.

54 หน้าว่าง



Chapter 5

The framework of guidance

56 หน้าว่าง



Introduction

- 5.1 The conduct of research related to healthcare is subject to a wide range of national and international guidance, guidelines, declarations and regulations (which we will call guidance, except for those regulations which have the force of law). The international guidance has formed the basis for the national guidance adopted in many countries. In general, the guidance covers a wide range of activities in research involving human participants. In Chapter 4, we set out four principles that should guide decision-making in the conduct of research related to healthcare in developing countries, which is sponsored by other, developed countries: the duty to alleviate suffering, the duty to show respect for persons, the duty to be sensitive to cultural differences, and the duty not to exploit the vulnerable. These principles are reflected in the various forms of guidance but are sometimes expressed in different ways. For example, respect for persons is sometimes expressed more narrowly as respect for individual autonomy. The duty to alleviate suffering is sometimes referred to in terms of beneficence, or a duty to benefit other people, and the duty not to exploit the vulnerable encompasses guidance expressed in terms of fairness and justice.
- 5.2 In addition, two common themes arise in the various forms of guidance. The first is the need for research to be based on sound scientific principles, on knowledge derived from laboratory and animal experiments, if appropriate, and on a sound understanding of the scientific literature. The second is the need to ensure that the results of research are accurately reported and published, that publication can only take place where it can be demonstrated that ethical principles relevant to the conduct of research have been observed, and that negative as well as positive results are reported.
- 5.3 Over recent years, there has been increasing criticism of much of the guidance which exists on two counts. First, while such guidance sets out the fundamental ethical principles relevant to the conduct of clinical research on human participants, it is too general in nature to address many of the specific and often controversial issues that are raised by such research. For example, guidance about the standards of care which should be used in clinical trials and the availability of treatment after a trial is over is set out in very general terms and has been subject to varying interpretations.¹
- 5.4 Secondly, the various forms of guidance, whether international or national, in many instances do not take into account the special circumstances that attend research undertaken in developing countries and sponsored by developed countries. In addition developing countries often have little or no relevant national guidance. In such situations, where research is externally sponsored, there is a danger that the conduct of the research may fail to reflect the cultural and social values of those from the developing countries who participate. In this chapter, we review the broad framework of guidance which concerns research related to healthcare and consider how the specific issues raised by externally-sponsored research are addressed.

The historical context

- 5.5 During the last century, there have been a number of notorious cases in which participants have been harmed as a consequence of unethical clinical research. The Nuremberg Code was formulated in 1947 following the Nuremberg trials, at which a number of Nazi researchers were convicted. The trials revealed that research on human beings had been conducted by Nazi physicians in Germany without due regard to the welfare or, indeed, the survival of the

1 In the debate concerning the 'standard of care' in the perinatal HIV transmission studies (see Box 1.2), both sides cited the CIOMS 1993 guidelines to support their position. Debate centred on the question of whether the 'best proven diagnostic and therapeutic method' (Article II:3 of the 1996 Declaration of Helsinki) should take local resource considerations into account.

participants. The central feature of the Nuremberg Code was the protection of the integrity of the person participating in research. The Nuremberg Code was endorsed by the World Medical Association (WMA), which published the Declaration of Helsinki in 1964. The Declaration, which has been revised five times to date (Table 5.1 and Appendix 1), sets out the principles to be observed in research on human participants and has become the cornerstone of research related to healthcare. Its standing is such that the principles enshrined in it have been incorporated into many of the forms of guidance that have subsequently been drawn up to govern the conduct of research related to healthcare (see Table 5.1 for international guidance and Appendix 1, Table 1 for national guidance).

Table 5.1**International guidance for the conduct of research related to healthcare**

Year	Organisation	Title
1947	War crimes tribunal at Nuremberg	Nuremberg Code
1948	United Nations General Assembly	Universal Declaration of Human Rights
1964	World Medical Association (WMA)	Declaration of Helsinki (1)
1975	WMA	Declaration of Helsinki (2) Tokyo
1983	WMA	Declaration of Helsinki (3) Venice
1989	WMA	Declaration of Helsinki (4) Hong Kong
1991	CIOMS/WHO	International Guidelines for Ethical Review of Epidemiological Studies
1993	CIOMS/WHO	International Ethical Guidelines for Biomedical Research Involving Human Subjects (Under revision in 2001–2)
1995	WHO	Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products
1996	WMA	Declaration of Helsinki (5) South Africa
1996	International Conference on Harmonisation (ICH)	Harmonised Tripartite Guideline. Guideline for Good Clinical Practice
1997	Council of Europe	Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine
1997	UNESCO	Universal Declaration on the Human Genome and Human Rights
2000	European Union	Charter of Fundamental Rights of the European Union
2000	UNAIDS	Ethical Considerations in HIV Preventive Vaccine Research
2000	WHO	Operational Guidelines for Ethics Committees that Review Biomedical Research
2000	WMA	Declaration of Helsinki (6) Edinburgh
2001	European Parliament and Council of the European Union	Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

International guidance for the conduct of research

- 5.6 The potential risk of harm to participants in research related to healthcare has led to widespread agreement that rigorous safeguards should be established irrespective of the geographic and economic setting in which it is undertaken. The present regime of guidance has developed largely in response to problems that have been encountered during the evolution of research related to healthcare. The major sources of international guidance have undergone, or are in the process of undergoing, revisions and development, but these revisions have generally been initiated to address specific shortcomings.
- 5.7 The implementation of guidance is the responsibility of those who are in contact with, or responsible for, participants in research. They will include government officials, aid agencies, institutional researchers, administrators and researchers, public and private sponsors of research, the senior management of companies, and research ethics committees. Ultimately, responsibility for observing and applying the guidance falls to those actively engaged in carrying out research involving human participants in the clinic, ward, laboratory or elsewhere. It is therefore important that guidance is written in terms which encourage consistent interpretation and which can be applied with confidence.
- 5.8 The guidance ranges from guidelines which claim general applicability, such as the Declaration of Helsinki and the guidelines of the Council for International Organizations of Medical Sciences (CIOMS)² to those with more narrow remits such as those set out in the **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)** which apply to the pharmaceutical industry, or **Ethical Considerations in HIV Preventive Vaccine Research** published by UNAIDS, which apply specifically to research into vaccines for a single disease (HIV/AIDS). In the next two sections, we consider how the Declaration of Helsinki and the CIOMS Guidelines apply in the context of research sponsored by developed countries and conducted in developing countries.

The Declaration of Helsinki

- 5.9 When the Declaration of Helsinki was published in 1964, the scope of its provisions was considered to be comprehensive. The Declaration established a set of basic principles from which were derived some general rules of conduct. The current revision (2000) recognises that the purpose of biomedical research involving human participants must be to 'improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease' and further, that medical progress is based on research that must at some stage involve human participants (see Box 5.1).
- 5.10 According to the current version (2000) of the Declaration, any research carried out involving human participants must be based upon sound scientific principles, and according to a properly formulated protocol for the study that has been subjected to the scrutiny and advice of an independent committee (i.e. a research ethics committee). The Declaration recognises the fact that most interventions – diagnostic, therapeutic and preventative – and especially those involving biomedical research, involve hazards and that the issues of risk and hazard must be addressed. It notes that when research involves healthy volunteers, special care must be taken to determine if the objective of the research outweighs the inherent risks and burdens to participants. The Declaration pays particular attention to the problems that may arise where research is combined

2 The guidelines were developed in collaboration with WHO.

BOX 5.1 Revisions to the Declaration of Helsinki

The Declaration of Helsinki has been revised five times by the WMA since its initial adoption in 1964. The revision in 1996 was accompanied by considerable debate and within a year, the American Medical Association (AMA) had proposed another significant revision. In addition to including a consideration of research in developing countries, the draft revision amended or expanded guidance relating to consent and review of the ethics of research, the involvement of pregnant women in research, possible conflicts of interest, data and confidentiality, and the publication of research results.

As the Declaration is considered to be the pre-eminent guidance on ethical principles in research relating to healthcare, there was criticism of the process for such a substantial revision of the Declaration, which had been restricted to members of the WMA. In response to this criticism, the draft revision proposed by the AMA was circulated for public comment. Concerns were expressed that a number of protections for participants in research were being minimised or removed. These included provisions relating to the standards of care provided to participants in research, responsibility for participants in research and publication of research results.¹ Those in favour of substantial revision argued that these provisions and others were not relevant to a number of situations in research, and were frequently breached. It was proposed that the guidance be updated so that it took greater account of current practice. A counter-argument was that it was the current practice that was unethical and the guidance needed only minor revision. Rather than substantially rewriting the fundamental guidance relating to research related to healthcare, it was claimed that the Declaration should continue to evolve slowly, with minimal amendments, and focus on setting out fundamental principles, about which there was broad agreement. Guidance about the application of principles could then be provided in accompanying commentaries, which could be updated more frequently.²

The revision proposed by the AMA was rejected and the WMA charged a committee with the task of putting together a new draft. This was circulated for comment, and adopted as a revision to the Declaration at the WMA meeting in Edinburgh in 2000. It was greeted with approval from critics of the AMA draft.³ However, a number of organisations have since claimed that paragraph 29 (concerning standards of care provided to participants in research) and paragraph 30 (concerning what happens once research is over) of the revised Declaration are inappropriate. The WMA has recently published a note of clarification for paragraph 29 (Table 5.2).

- 1 Anon (1999) Helsinki Declaration revising continues, **Bulletin of Medical Ethics**, 146 3–5.
- 2 Review (1999) Revising the Declaration of Helsinki: a fresh start, **Bulletin of Medical Ethics**, 151 13–17.
- 3 For example, commentators from Public Citizen asserted that the revised Declaration meant that ‘researchers [would now] have no choice but to provide scientifically proven interventions-regardless of where the research is conducted’ (see letter to the editor, **Washington Post**, 17 October 2000).

with professional care. Whilst a physician can combine medical research with clinical care (see Box 5.2), this is only justified by the potential benefits which may accrue for the patient and the group to which he or she belongs and subject to special provisions, including an assessment of the benefits, hazards and discomforts of the new procedure along with a comparison with the advantages of the best current methods, if such exist.³

- 5.11 The Declaration states that the hazards attendant upon the project must be predictable and where they outweigh the potential benefits, the research should not proceed. In carrying out such an assessment, the interests of the subject must always prevail over the interests of science, industry, or society. Furthermore, the Declaration states that participants always have the right to safeguard their integrity and their privacy. The importance of these considerations is that they lead on to the central requirement: that before research related to healthcare can be carried out involving human participants, the participants must first be adequately informed about all relevant aspects of the study including its aims, procedures, attendant risks and hazards and the potential

3 World Medical Association (2000) **Declaration of Helsinki**: paragraphs 28–29 (see Appendix 1).



benefits and discomforts, and then their consent sought. Informed consent must be freely given by the participants. The issue of consent is discussed in Chapter 6.

5.12 As noted in Chapter 1, there has been a major debate over whether the standard of care provided to participants in one specific form of research, the clinical trial,⁴ in a developing country should always involve that diagnostic, prophylactic or therapeutic method which has been proved to be the best. Such methods may be beyond the means of those in the developing country. In such a case, it has been argued that it is acceptable to conduct research on new treatments by comparing them with alternative treatments or placebo rather than the best treatment. The current revision of the Declaration states that ‘The benefits, risks, burdens and effectiveness of a new method [of treatment] should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods’ (paragraph 29). This does not, of course, exclude the use of placebo, or of no treatment, in studies where no proven prophylactic, diagnostic or therapeutic methods exists. But, it appears to stipulate that the best treatment be made available by way of comparison to all other circumstances. Following concerns that paragraph 29 could not be implemented in developing countries, the World Medical Association published a ‘clarification note’ in 2001. The note states that in general placebo-controlled trials should only be used in the absence of existing, proven therapy. However two exceptions are outlined:

- where for compelling and scientifically sound methodological reasons [the use of placebo-controlled trials] is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm (see Appendix 1).

This issue is discussed in depth in Chapter 7.

5.13 The question of what care a participant should receive once research (combined with medical care) is over has also proved controversial. Guidance on this point was included in the current version (2000) of the Declaration of Helsinki for the first time. Paragraph 19 of the Declaration states that ‘Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.’ Paragraph 30 states that ‘At the conclusion of the study, every patient entered into the study should be

BOX 5.2 Distinguishing between therapeutic and non-therapeutic research

The practice of distinguishing between therapeutic and non-therapeutic research¹ has now largely been abandoned because of a growing recognition that most trials involving therapeutic research contain non-therapeutic components and we have therefore not attempted to make such a distinction in the Report.² In the following chapters, much of the discussion focuses on research that contains a therapeutic component (see especially Chapters 7 and 9). However, the discussion of principles underlying research, and in some cases the conclusions and recommendations (particularly in Chapters 6 and 8) are also relevant to research without a therapeutic component.

- 1 We use the term ‘therapeutic research’ to indicate research having the potential to produce a real and direct benefit for the participants and ‘non-therapeutic research’ to mean research without such potential.
- 2 Nuffield Council on Bioethics (1999) **The ethics of clinical research in developing countries**, Nuffield Council on Bioethics, London.

⁴ See the glossary for a definition of clinical research and clinical trials.

assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.' We give detailed consideration to this issue in Chapter 9.

The CIOMS guidelines

- 5.14 CIOMS, in collaboration with WHO, recognised the special circumstances which arise when applying the Declaration of Helsinki to research undertaken in developing countries, and proposed guidelines to address them in 1982. These guidelines sought to direct the conduct of research involving human participants in a way that would recognise the social, economic, legal, regulatory and administrative arrangements that exist in developing nations. They have been widely adopted throughout the world. However, with the increasingly transnational nature of research, and the growing incidence of research involving large-scale clinical trials of medicines and vaccines, particularly following the emergence of HIV and AIDS, further revisions are under consideration.
- 5.15 In producing revisions, CIOMS/WHO also took into account the growing importance of epidemiological research for public health. In 1991 the **International Guidelines for Ethical Review of Epidemiological Studies** were published. These in turn informed the revised WHO/CIOMS guidance published in 1993 entitled **International Ethical Guidelines for Biomedical Research Involving Human Subjects**. Primacy was given to the protection of the rights and welfare of participants in research, and particularly those considered to be vulnerable. This guidance is currently being modified and the revised edition is expected to be published in 2002.

Other international guidance

- 5.16 Two further sources of guidance are routinely consulted with regard to the ethical conduct of research. Both draw on the Declaration of Helsinki. First, the **Guidance on Good Clinical Practice**⁵ provides unified technical standards for clinical trials so that clinical data generated are mutually acceptable to regulatory authorities in the EU, the US and Japan. Secondly, the **Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products**⁶ from WHO lay down basic requirements for the ethical conduct of research. In addition, guidance entitled **Ethical Considerations in HIV Preventive Vaccine Research**⁷ was published in 2000 by UNAIDS. Although designed for, and applied in the context of the development of vaccines, the guidance could be of relevance more generally.

National guidance for the conduct of research

- 5.17 The ethical principles outlined in Chapter 4 have been widely adopted at the national as well as the international level by those developed and developing countries which have established guidance to cover research involving human participants in their own territory. Guidance adopted

5 International Conference on Harmonisation (ICH) (1996) **Harmonised Tripartite Guideline. Guideline on Good Clinical Practice**.

6 World Health Organization (WHO) (1995) **Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products**.

7 UNAIDS (2000) **Ethical Considerations in HIV Preventive Vaccine Research**. UNAIDS Guidance Document, UNAIDS, Geneva.

in Denmark and Uganda is shown in Box 5.3. Some national guidance has the force of law, whilst other guidance is enforced by funding agencies for research as a condition of making a grant, or is simply voluntary codes of practice drawn up by national professional bodies, having persuasive force only. In most cases, the guidance applies within the country or its territories. In some cases, there are specific provisions relating to particular indigenous populations.⁸ In New Zealand the importance of ensuring that research related to healthcare contributes to health development in Maori communities has been recognised.⁹ Similarly, in Australia the National Health and Medical Research Council (NHMRC) has addressed the ethical issues that arise in connection with research related to health in Aboriginal and Torres Strait Islanders.¹⁰ In other cases, there is specific recognition of the need to take differences in language and culture into account, for example, in the context of obtaining consent.¹¹

5.18 In a few cases guidance is explicitly applicable to research carried out under the auspices of national agencies in other geographical areas.¹² For example the US National Institutes of Health (NIH) **Guidelines for the Conduct of Research Involving Human Subjects**

at the NIH¹³ have been made explicitly applicable to research sponsored from within the US but carried out elsewhere.

BOX 5.3 Examples of national guidance: Denmark and Uganda

Denmark has published two laws on the ethics of research related to healthcare involving human participants.¹ These lay down the ethical principles to be considered by a national system of regionally-based committees carrying out review of the ethics of research with a majority of lay members. Since being established in 1980, all projects on healthcare in developing countries involving Danish scientists or Danish public funds have been evaluated under this system, and by the research ethics committees in the host country.

In 1997, **Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda** were published.² These were the outcome of a process which began in 1994 to examine Ugandan guidance for the review of scientific research proposals involving human participants. The Guidelines set out general provisions for the protection of participants, along with requirements for institutional review committees, informed consent (including additional protections pertaining to vulnerable populations), and for monitoring and publishing research.

- 1 Act no. 503 of 1992 and Act no. 499 of 1997.
- 2 National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference) (1997) **Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda**, National Consensus Conference, Kampala, Uganda.

8 For example, the National Health and Medical Research Council of Australia (NHMRC) (1999) **National Statement on Ethical Conduct in Research Involving Humans**.

9 The guidelines also emphasise the value of research partnerships between researchers and Maori communities on issues important to Maori health and the importance of encouraging them. To achieve these objectives, in 1998 the Maori Health Committee (MHC) of the Health Research Council of New Zealand published 'Guidelines for Researchers on Health Research involving Maori'. These were based on provisions laid down in the 19th century in the Treaty of Waitangi between the New Zealand government and Maori people. They place considerable emphasis on consultation with the Maori community to ensure that researchers did not offend cultural and tribal sensitivities in the course of research projects.

10 NHMRC published 'Guidelines on Ethical Matters in Aboriginal and Torres Strait Islander Health Research' in 1991. These are directed at the Institutional Ethics Committees (IECs) in Aboriginal and Torres Straits Islander-controlled organisations which deal with ethical approval of project proposals from researchers in these organisations. As with the New Zealand guidelines, these emphasise the importance of consultation with the community-controlled health services and consent of the community for the research.

11 See the Brazilian 'Resolutions 196/1996, 251/1997 and 292/1999'.

12 See, for example, the US NIH (1995) **Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health**, and, in the case of the use of US Federal agency funds **Code of Federal Regulations Title 45 Public Welfare - Part 46 - Protection of Human Subjects** (1991).

13 US NIH (1995) **Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health**.

- 5.19 In the US, the ethical issues which arise when clinical research sponsored by the US is undertaken overseas were given detailed consideration in the US National Bioethics Advisory Commission's (NBAC) report entitled **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (2001)**. The Commission expressly discussed the problems that may arise when clinical research that is subject to US guidance is undertaken in developing countries. The report points out that this form of collaboration in research, although desirable, may cause controversy, particularly about the nature of the collaboration and the distribution of any resulting benefits. It also draws attention to the fact that 'Such controversies are perhaps more likely to occur when the nations involved do not share the same cultural, economic, political, and ethical perspectives, or when they are at different stages of development'.¹⁴
- 5.20 The NBAC Report emphasises the ethical and logistical problems that arise where research related to healthcare in developing countries is externally sponsored. The studies in question might simply be one way of helping the host country to address a problem in public health, or they might reflect an assessment by a research sponsor that the foreign location is a more convenient, efficient, or less problematic site for conducting a particular study or clinical trial. They might also represent a joint effort to address an important concern for healthcare faced by both parties'.¹⁵ The NBAC Report draws attention to a more fundamental question regarding collaboration in research, particularly that which involves studies in the developing world: whether the existing rules drawn up by the US to regulate researchers working in the US are 'appropriate in the context of international research, or whether they unnecessarily complicate or frustrate otherwise worthy and ethically sound research projects'.¹⁶

The enforcement of guidance

- 5.21 As discussed earlier in the Chapter, most of the existing guidance on research related to healthcare does not have the force of law. However, the US Policy for the Protection of Human Subjects, which was inspired by the Belmont Report,¹⁷ has legal force by being incorporated into the US Code of Federal Regulations. A few other countries, such as Denmark, have enshrined the main ethical principles governing medical research in law (see Box 5.3). Other guidance, such as the Council of Europe's **Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine**¹⁸ (Table 5.1) mentioned above, derive their authority through treaty obligations imposed on signatory nations.

14 National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: p. 1.

15 NBAC (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: p. 1.

16 NBAC (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: p. 1.

17 The US National Research Act (1974) established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the Commission's charges was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioural research involving human subjects and to develop guidance to ensure research is conducted in accordance with these principles. The Belmont Report represented a summary of the basic ethical principles identified by the Commission in the course of its deliberations, see The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) **The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research**, Department of Health, Education, and Welfare, Washington, DC.

18 The Convention, which was adopted in 1997 to bring about the harmonisation of the standards in use within different European countries which have ratified the Convention, goes beyond the issues surrounding research on human participants and deals with a much wider range of medical practices, including issues that will arise out of genomics research and the clinical application of genetics and individuals' access to treatment. The Convention recognises, for instance, that standards are to be applied within local contexts and circumstances. A working party of the Council of Europe has recently prepared a detailed draft additional protocol on biomedical research that will be legally binding on all signatories within European States after its launch. In June 2002, the Steering Committee on Bioethics will review the Protocol. If agreed, it will then be submitted to the Parliamentary Assembly for consultation prior to submission for final adoption by the Committee of Ministers.

- 5.22 Most of the existing guidance, however, has merely persuasive force and is only enforceable through sanctions imposed on members of the profession or group which was responsible for the particular guidance. The Declaration of Helsinki, produced by the WMA, only binds physicians. Similarly, the CIOMS guidelines only bind members of the signatory organisations. Many involved in research related to healthcare today, however, are not members of the medical profession and thus may not be accountable under these guidelines.
- 5.23 In other cases, guidance can be enforced by the application of sanctions which will directly affect researchers who do not observe the operating standards and principles laid down. Guidance published by grant-giving agencies, for example, derives its authority from the fact that, unless it is adhered to, financial support for research will be withdrawn or not awarded. Pharmaceutical companies which contravene the guidance contained in the ICH's **Technical Requirements for Registration of Pharmaceuticals for Human Use** will find it difficult, if not impossible, to get a new medicine accepted by the regulatory authorities responsible for issuing licences to market products.
- 5.24 It is one thing to have guidance, it is another to interpret and apply it. Guidance is liable to different interpretations in different contexts. Furthermore, it is in the nature of such guidance that it does not seek to be comprehensive, given the increasing range of contexts that it is required to cover. For guidance to have the force of law, where it currently does not, a different approach would have to be adopted. The language would have to be clear and relevant to and applicable in a range of contexts and situations. To date this has not been achieved, as was highlighted in many of the responses to the consultation exercise carried out by the Working Party (Appendix 5). It may in fact be difficult to achieve given political and social pressures which come into play when, as a first step, attempts are made to harmonise and clarify the various elements of guidance. Meanwhile, whether or not guidance should have the force of law, there are obviously gaps in existing forms of guidance.
- 5.25 We have already emphasised that the external sponsors have a duty not to exploit the vulnerable when undertaking research related to healthcare in developing countries. The main aim of the guidance described in this chapter is to protect participants in research from harm, and particularly in the case of developing countries, from exploitation. In practice, researchers and sponsors are often confronted with guidance which is often generalised and even contradictory. Nor does the guidance generally take into account the special circumstances which characterise externally-sponsored research in developing countries. How best then can these countries protect their interests? We suggest two approaches that could be followed in which both developed and developing countries have a role. First, education and training can be arranged to develop expertise in developing countries for the purpose of active participation in the review of the ethics of externally-sponsored research. Secondly, the development of national guidance for the protection of participants in research offers developing countries the opportunity to set their own standards of protection in the light of international guidance. We consider each of these two approaches in turn.

Training

- 5.26 Guidance on the ethical conduct of research related to healthcare will be of little real value unless it can be understood and applied by sponsors of research, researchers and members of research ethics committees. Provision must be made for the education and training of those involved in research related to healthcare to ensure that guidance on ethical conduct is clearly understood and implemented. We strongly urge that such education and training should be made available not only to researchers and others in developing countries, but also to researchers in developed

countries so that a common understanding is established. **We conclude that in any revised or new guidance the provision of training in the ethical conduct of research should be a requirement placed on all involved in the sponsorship of research in developing countries.**

- 5.27 Research related to healthcare is not conducted exclusively by medically qualified practitioners. On the contrary, much research in this area is now necessarily multi-disciplinary. Researchers may be biochemists, molecular and cellular biologists, geneticists, psychologists, sociologists, anthropologists or others. All of these should be brought within the ambit of the guidance on ethics that address responsibilities to research participants. **We recommend that national and international sponsors of research ensure that provision is made for education and training in the ethics of research of all of those professionals involved in research related to healthcare to ensure that the requirements of relevant guidance on ethics are met.**

The development of national guidance

- 5.28 As we noted above, researchers, sponsors and others who are involved in research related to healthcare are faced with diverse and sometime conflicting guidance. A number of developing countries (and many developed countries) have responded to this difficulty by developing their own national guidance to provide a framework for the review of the ethics of research related to healthcare in their countries. Such guidance, which should be based on an interpretation of the international guidance set out in this chapter, generally applies to both externally-sponsored research and internally-funded research. Developing countries which have taken this step include South Africa, Uganda, Nepal, Thailand, India, and Brazil (Appendix 1, Table 1). The development of expertise to formulate national guidance may also require education and training. **We encourage developing countries to take account of existing international and national guidance and to create national guidance for its clear and unambiguous application.** We take the view that, taken together, the development of national guidance and the strengthening of the process of review of the ethics of research related to healthcare will afford a further layer of protection to participants in externally-sponsored research studies and should be priorities for developing countries and sponsors of research.

The issues

Section 3

68 หน้าว่าง



Consent

Chapter 6

70 หน้าว่าง



Introduction

- 6.1 Respect for persons is a fundamental moral duty. In research relating to healthcare, this duty requires that we do not act against a person's wishes. His or her consent to participate in research must thus be obtained. The duty upon those conducting research ordinarily to obtain consent is widely recognised in national and international guidance and in legislation (see Box 6.1).¹ The three elements of consent reflected in ethics, national legislation and human rights law are that it must be informed, given voluntarily, and given by a person competent² to do so. In this chapter we will focus on two elements of consent which are particularly relevant to externally-sponsored research conducted in developing countries: the provision of information to participants in research; and the requirement that consent to research be given voluntarily. Appropriate means of documenting consent to take part in research will then be considered.
- 6.2 When externally-sponsored research is conducted in developing countries, a range of issues arise in seeking consent to take part in research. With regard to informing potential participants, concepts that are common in research, such as the idea of randomisation, or of using placebos, may be unfamiliar to the culture in which the research is being conducted. As regards the voluntariness of consent, in some communities it is common for a spouse or senior member of a family to assent to healthcare (and by extension, to research) on behalf of a woman or adult children (see paragraph 3.18). In addition, access to better healthcare and other benefits which may accrue from taking part in research may act as powerful inducements, casting doubt on the true voluntariness of a participant's consent.
- 6.3 In research, in addition to their responsibilities to individual participants, researchers are seeking to conduct scientifically sound research that will provide generalised information that can improve healthcare. When medical care is combined with research, researchers may make different choices about clinical measures than they would if the participants' best interests were their only concern. For example, during research, healthcare workers may administer placebos or take blood samples for tests that will not benefit participants directly, in order to obtain information. The potential conflict between the dual roles of healthcare providers in such circumstances means that the process for obtaining consent to research must be rigorous and that participants must be made aware of the dual purpose of research before being asked to consent to it. Conversely, when research does not contain any therapeutic component, this fact must also be made clear to prospective participants.

Information

- 6.4 A prospective participant in research must be provided with information about the proposed research before any consent to participate can be considered to be valid. The ethically significant requirement is that consent to research be *genuine*.³ Ensuring that consent is genuine

1 US Regulations make provision for waiver of consent under four conditions: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation (45 CFR 46.116d). The UK Medical Research Council 1998 guidance entitled 'Guidelines for Good Clinical Practice in Clinical Trials' paragraph 2.9 states that 'freely given informed consent should be obtained from every participant prior to clinical trial participation' though this does acknowledge that situations may exist where this is not possible (e.g. emergency settings) and in such cases, procedures agreed in existing guidelines should be followed provided favourable opinion has been given by the appropriate independent ethics committee. The UNESCO's Universal Declaration states that 'limitations to the principle of consent and confidentiality may only be prescribed by law, for compelling reasons within the bounds of public international law and the international law of human rights' (Article 9).

2 A person is considered to be competent if they are able to understand information about the proposed research.

3 Nuffield Council on Bioethics (1995) **Human Tissue: ethical and legal issues**: Paragraph 6.20, Nuffield Council on Bioethics, London.

BOX 6.1 Examples of guidance on consent

The Helsinki Declaration (2000 revision) requires that each potential subject must be adequately informed about:

- the aims of the study and methods to be used;
- the sources of funding and possible conflicts of interest;
- the institutional affiliations of the researcher;
- the anticipated benefits and potential risks and the follow-up of the study;
- the discomfort it may entail; and
- the right to abstain from taking part in the study, or to withdraw from it at any time, without any reprisals.¹

The CIOMS/WHO 1993 Guidelines set out, in some detail, the 'essential information' that must be provided to research participants.² These go further than the Declaration of Helsinki and include:

- the alternative procedures or treatments available;
- what responsibility, if any, lies with the investigator to provide medical service to the subject;
- provision of free treatment for injuries related to research.

A detailed list of the duties of investigators in obtaining consent which is properly informed is provided, including:

- encouraging the participant to ask questions;
- avoiding possible deception; and
- obtaining new consent if the conditions or procedures involved in the study change.³

1 World Medical Association (WMA) (2000) **Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects**, adopted by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; paragraph 22.

2 See CIOMS in collaboration with WHO (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects: Guideline 2**. This should be regarded as a minimum and the guidance in the commentaries on several of the other guidelines outlines circumstances where additional types of information should be conveyed.

3 CIOMS in collaboration with WHO (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects: Guideline 3**.

requires care in detecting a lack of consent. The apparent genuineness of consent can be defeated by a number of circumstances, including coercion, deception, manipulation, deliberate misdescription of what is proposed, lack of disclosure of material facts, or conflicts of interest.

6.5 To obtain genuine consent, health professionals must do their best to communicate information accurately and in an understandable and appropriate way. The information provided to participants must be relevant, accurate and sufficient to enable a genuine choice to be made. It must include such matters as the nature and purpose of the research, the procedures involved, and the potential risks and benefits. National and international guidance sets out the factors which prospective participants must be informed of (see Box 6.1).

6.6 Requirements of particular relevance to externally-sponsored research conducted in developing countries include the need to ensure that participants be provided with information about the study in a language that they can understand, and at their level of comprehension.⁴ The importance of allowing potential participants the time to ask questions, obtain answers and to reflect and give due consideration to their participation is also emphasised.⁵

6.7 An awareness of the social and cultural context in which the research is to be conducted is required, so that communities and individuals can be informed of any

4 For example, the commentary accompanying Guideline 2 of the CIOMS in collaboration with WHO (1993) guidance explicitly states that 'Informing the subject must not be simply a ritual recitation of the contents of a form. Rather, the investigator must convey the information in words that suit the individual's level of understanding'.

5 See, for example, National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference (1997) **Guidelines for the Conduct of Health Research involving Human Subjects in Uganda**: p. 32; Indian Council of Medical Research (2000) **Ethical Guidelines for Biomedical Research on Human Subjects**: General ethical issues, 2i.

aspects of the research that may cause them particular concern. These may include such matters as the amount of blood to be taken, or whether participants will be physically examined by researchers of the opposite sex. The process of informing participants about research must also provide opportunities for individual participants to ask about such matters as whether the research may affect their ability to carry out their livelihood. Consent may sometimes need to be sought in the presence of another person, or group, so that the individual feels supported, and more able to ask questions or voice concerns. In other circumstances, privacy may be essential; for example if the prospective participant wants to discuss confidential issues, such as HIV status, with the researcher.

- 6.8 Healthcare professionals should respect the limits of individuals' understanding and capacity to deal with difficult information and allow time for them to reflect and ask questions. For example, participants may have little understanding of the biological processes that take place in their bodies, or have different beliefs about the causes of disease, which make it more difficult to comprehend the information given. If all reasonable care is exercised, genuine consent may be given.

Issues which may arise when informing participants about research

- 6.9 In some developing countries, during routine clinical care, information about a diagnosis of a serious disease such as cancer may be provided to a patient's family, rather than to the patient.⁶ In such circumstances, the requirement that genuine consent be given to participation in research into appropriate cancer treatments will conflict with standard medical practice, which is to withhold the diagnosis of cancer from a patient.
- 6.10 In some cultures it is customary for a physician to advise a patient which treatment to take, rather than discuss various treatment options. In Vietnam, for example, it has been suggested that: 'it is unacceptable for a physician to openly express uncertainty with regard to what is the best treatment.'⁷ In such circumstances, it has been argued that it is not appropriate to comply with the requirement that participants be informed about the options for treatment which are available, and that there is uncertainty about which will prove to be the best.⁸
- 6.11 In Chapters 3 and 4 we discussed the need to be sensitive to the cultural context in which research is conducted. However, this does not mean that cultural practices must be accepted uncritically. In the circumstances outlined above, there is a tension between the requirement that genuine consent to research be obtained from participants and cultural contexts in which giving certain information is not customary. The Working Party has considered these competing interests and has concluded that obtaining genuine consent to research from participants is vital in ensuring that respect for persons is promoted. Without appropriate information, participants in research may be harmed by being exposed to risks or dangers that they would prefer to avoid. In addition, they will be denied the opportunity to learn more about their condition, possible treatments, and any beneficial outcomes of the research. Consequently, when research is conducted in contexts in which the information about diagnoses and options for treatment is not normally provided, care and sensitivity will be required to design appropriate consent procedures, so that participants receive appropriate information about research and genuine consent may be given.

6 See, for example, Moazam F (2000) Families, patients, and physicians in medical decisionmaking: a Pakistani perspective, *Hastings Center Report*, November–December: 28–37 and Macklin R: The doctor–patient relationship in different cultures, in Macklin R (1999) *Against Relativism. Cultural Diversity and the Search for Ethical Universals in Medicine*, OUP, New York.

7 Love RR and Fost NC (1997) Ethical and regulatory challenges in a randomized control trial of adjuvant treatment for breast cancer in Vietnam, *Journal of Investigative Medicine*, 45(8) 423–31.

8 Love RR and Fost NC (1997) Ethical and regulatory challenges in a randomised control trial of adjuvant treatment for breast cancer in Vietnam, *Journal of Investigative Medicine*, 45(8) 423–31.

Understanding information

6.12 A number of methods have been used by researchers in developing countries to ensure that information about research has been provided to participants in an appropriate manner. These include:

- providing information to participants at meetings, so that they have an opportunity to discuss the proposed research with others and pose questions for clarification
- providing information through health workers (and particularly female health workers when the research will involve women), rather than physicians so that participants feel more able to discuss and ask questions
- providing information about a research project in various ways that are appropriate to the community (i.e. in parts of Africa, information has been supplied on audio or video tape, on the radio and through ballad singers)
- providing information over a period of time, so that prospective participants have time to consider it and raise questions.

We concluded in Chapter 3, that consultation with the community in which research is to be conducted will be required to determine which methods of providing information will be most appropriate for a given research project. In some communities, particular care will need to be taken to ensure that the methods of providing information and aiding understanding which are adopted will ensure that the information will reach all members of the community. For example, if public meetings are used, it must be borne in mind that young women may feel unable to ask questions during such a meeting.

6.13 Information about research should be provided in a form that is likely to be comprehensible to a prospective participant. In some circumstances, healthcare workers, some of whom may have been recently recruited, will be responsible for explaining the research to prospective participants. Clearly, researchers will need to provide appropriate training to ensure that healthcare workers understand the research and can pass on accurate and comprehensible information.

6.14 A number of methods have been used by researchers to assess whether participants in research have understood information provided about the proposed research. For example, prospective participants may be asked to pass a test before consenting to participate in the research. Such tests are designed to ensure that the relevant information about the research has been understood. Alternatively, following the provision of information, prospective participants may be asked to explain what they have understood about the research.

Complex and novel concepts

6.15 Some concepts used in research may be difficult to explain in a understandable manner, particularly in populations with entirely different beliefs about the causes of illness and little familiarity with biomedicine. In such circumstances, researchers will need to consult communities to determine how concepts can be explained in a comprehensible manner. One example is to incorporate local belief systems into the process of providing information. For example, the researchers might say: 'Although I as a doctor believe that the disease is caused by germs (i.e. a virus or bacterium), I understand that you believe that it is caused by a demon. I respect the fact that you have this belief and I should like you to try this medicine to remove the disease. Removing the disease is more important to us both than whether we think it is caused by germs or a demon.' Some biomedical researchers resist this approach on the ground that biomedical interventions should not perpetuate what they regard as 'unscientific' or 'superstitious' beliefs and

practices. However, in some circumstances it will be possible to strike a balance between such a stance and the harnessing of local beliefs in the interests of improving participants' understanding of research.

6.16 Participants in research in developing (and developed) countries may find concepts such as randomisation, genetic research and placebos incomprehensible.⁹ Indeed, many languages will not have terms for such concepts. Researchers in developing countries have demonstrated that such concepts can be successfully explained, but again, care will be required to do so (see Box 6.2).¹⁰

6.17 In many developed countries, in response to the interests of relatively sophisticated populations and following concerns about legal liability, detailed and complex information is provided to prospective participants, setting out possible risks accompanying research. In both developed and developing countries such information may be poorly understood and, to the degree it may be understood, unduly alarming, particularly in populations with little experience of discussing possible side-effects or risks accompanying treatment.¹¹ For example, during the Working Party's fact-finding meeting in India, one physician noted that in rural areas the trust in doctors was so great that if a doctor described six possible side-effects of a treatment then participants often expected to experience them all.¹² Consequently, collaboration will be required with local researchers and representatives to ensure that information about risks and the likelihood of their occurrence is provided to participants in a comprehensible manner.

BOX 6.2 Good practice in explaining research concepts¹

To illustrate the principle of randomisation and the possibility that one of the vaccines might fail, in one research project a familiar agricultural example was used: the evaluation of fertilizers or of seed varieties on randomised plots, a procedure familiar to farmers in the area.

Another study required the concept of immunology and the role of immune cells to be explained. Immune cells were likened to people who guard houses, as a type of watchman, with blood depicted as containing particular kinds of watchman.

1 National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I**, National Bioethics Advisory Commission, Bethesda.

Voluntariness

6.18 As discussed above, for consent to be genuine, it must be freely given. In some societies in developing countries, it is considered inappropriate for an individual to be asked to consent to participate in research without the community, or leader(s) of the community, having been consulted first (see Chapter 3). In other groups, a family or leader(s) of the community may be

9 In one study in the UK an exploration of participants' understanding of randomisation showed that: (1) Most trial participants were able to recall and describe various aspects of randomisation, including the involvement of chance, comparison and concealed allocation, (2) The majority found the concept of randomisation difficult to accept and developed other accounts to make sense of their experiences, (3) The use of terms which have different meanings to lay and professional (such as trial and random) can cause confusion among participants, (4) Providing clear and accurate patient information is crucial, but to give truly informed consent, patients may need time to discuss the purpose of clinical trials and concepts such as randomisation. See Featherstone K and Donovan JL (1998) Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial, *BMJ*, 317 1177–80.

10 See National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I Report and Recommendations of the National Bioethics Advisory Commission**, Bethesda, Maryland, USA : 40–41, for description of innovative ways of presenting information to research participants.

11 See Marshall PA (2001) The relevance of culture for informed consent in US-funded international health research, in National Bioethics Advisory Commission (NBAC) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries**. See **Volume II Commissioned Papers and Staff Analysis** for a discussion of issues around disclosure of risk in informed consent.

12 Personal communication, Working Party fact-finding meeting.

BOX 6.3 The role of the community when consent is sought

Some national codes specifically address the role of the community and its leaders in the process of informing participants about research and obtaining consent. For example, the guidance in Brazil recognises the need to be sensitive to cultures and communities and requires that in the case of communities with a separate culture, including indigenous populations, prior consent must be obtained from leaders of the community before consent from prospective participants is sought. The importance of making efforts to obtain the consent of each participant in a study is also emphasised.¹

Guidance on research in New Zealand recognises in research with Maori communities the tribe and extended family groups have some authority over their members’ participation in research. The guidance, therefore, emphasises the need at all stages of a research project for consultation with the Maori communities who will participate in it.² However, this does not remove the need to obtain the consent of each participant in research.

Australian guidance requires that with research involving aboriginal and Torres Strait Islander communities there must be written evidence of the assent of the community, or justification why it has not been possible to obtain it.³ There must also be evidence of the process for obtaining the consent of each participant.

1 See, for example, Paragraph IV (3e) of the Brazilian Resolution No. 196/96 on Research Involving Human Subjects which states that ‘in communities with a different culture, including Indigenous communities, prior consent must be obtained from the community, through its leaders, without foregoing, however, efforts to obtain individual consent.’

2 The Maori Health Committee of the Health Research Council of New Zealand (1998) **Guidelines for Researchers on Health Research involving Maori.**

3 National Health and Medical Research Council of Australia (1999) **Guidelines on Ethical Matters in Aboriginal and Torres Strait Islander Health Research.**

expected to make decisions about participating in research on behalf of women and older children, who would make their own decisions in other societies. An additional factor which may affect the voluntary nature of consent to research is any inducements accompanying invitations to participate in research. These are considered in turn.

The assent/involvement of the community

6.19 In some societies it would be considered culturally inappropriate for researchers to ask individuals to participate in research without consulting the community or permission from community leaders. Three such situations can be distinguished:

- consultation is required with the community before individuals are approached about research
- permission from a leader(s) of the community is required before any research is discussed with the community or individuals
- the leader of the community is considered to have the authority to enrol participants in research.

6.20 In each of these circumstances, to seek consent from an individual without seeking assent from leader(s) of the community, or creating public acceptance of research, may be considered disrespectful and may harm relationships within that community and between a community and researchers. The role of the community in the process of obtaining consent is specifically recognised in some countries’ guidance on research (see Box 6.3).

6.21 The third of the situations set out in paragraph 6.19, where the leader(s) of the community or a senior family member customarily has the authority to make decisions on behalf of others, including whether they will participate in research, is the most problematic. In some developed countries, in limited circumstances and with strict safeguards, the law permits a proxy to consent to research on behalf of children and adults who do not have the capacity¹³ to make such

13 We use the term capacity to mean a participant who is competent to consent to research themselves, i.e. if they are able to understand information about the proposed research.

decisions themselves. However, as discussed in paragraph 3.18, the notion of consent on behalf of others is more widespread and ingrained within some cultures in developing countries.

6.22 We noted in Chapter 4 that we cannot avoid the responsibility of taking a view when the two aspects of respect – respect for culture and respect for persons – come into conflict with one another. We are of the view that the fundamental principle of respect for persons requires that participants who have the capacity to consent to research should never be subjected to research without such consent. Some prospective participants may choose to delegate to another, the decision about whether or not to participate in research. Where such delegation has not taken place, to allow others to make decisions on behalf of participants in research who have the capacity to consent themselves would be to deny that all people are moral equals and deserve to be treated in ways that promote their dignity and wellbeing. We conclude that assent from others may be necessary before research is conducted, but that it is not sufficient: individual participants must receive appropriate information about the research and should be asked to give consent. To ensure that individual participants can make up their own minds without undue communal pressure, anonymity for those who wish to decline to participate in research should be assured. **We recommend that, in circumstances where consent to research is required, genuine consent to participate in research must be obtained from each participant. In some cultural contexts it may be appropriate to obtain agreement from the community or assent from a senior family member before a prospective participant is approached. If a prospective participant does not wish to take part in research this must be respected. Researchers must not enrol such individuals and have a duty to facilitate their non-participation.** A summary of the reasoning behind this conclusion is given in Box 6.4.

BOX 6.4 Summary of arguments about genuine consent

The principle of respect for persons requires that we do not conduct research without their consent.

BUT

Sensitivity to other cultures requires that researchers pay attention to the context in which research is conducted, including customs and traditions.

NONETHELESS

Sensitivity to other cultures cannot override the central requirement of respect for persons, which requires that we refrain from conducting research without consent. This is a fundamental principle, which it is important to promote so as to empower vulnerable populations.

THEREFORE

Genuine consent to research must be sought from all participants in research.

AND

There is also a duty to develop or implement innovative practices with regard to providing information and to ensure that consent to research is freely given.

Refusing to participate in research

6.23 One respondent to our public consultation from South Africa, asked, ‘How can women – who are known, can be identified and found, and are dependent on the available health facilities which simultaneously function as research sites – be made to feel that their participation is voluntary?’¹⁴ The real significance of this question lies in the extent to which such women could feel free to say no to research. If consent to research is to be genuine, participants will need to be made

14 Response by the HIV/AIDS Vaccine Ethics Group (HAVEG) at the University of Natal, South Africa, to the Working Party’s Consultation.



aware that they may choose to refuse to take part, or withdraw at any time and that this will not affect their future healthcare.¹⁵ Consultation with local communities and researchers will be necessary to design an appropriate consent process that takes account of these matters. When concerns arise about whether or not participants feel able to decline to participate, it may be appropriate to have some form of external audit of the process for obtaining consent and its outcomes.

- 6.24 The Helsinki Declaration cautions that, where a subject is ‘in a dependent relationship with the physician or may consent under duress’, consent should be obtained by an independent physician. However, where participants have great respect for physicians and little awareness that they can refuse to participate in research, it may be immaterial whether it is a physician whom they know or an independent physician who asks for their consent. Researchers must take account of this respect for physicians and develop means to ensure that participants know that they can refuse to participate in research. In some circumstances it may be easier for participants to refuse to participate if they are speaking to a healthcare worker or interpreter, rather than a physician. Care must be taken, therefore, to ensure that research workers and interpreters realise that their role is to provide accurate information in an understandable manner to prospective participants, rather than to enrol as many participants as possible.

Inducements

- 6.25 Participants in research in developing and developed countries have a range of motivations for taking part in research (see paragraph 3.21). One motivation that may be offered to prospective participants is a benefit, such as a financial payment, or healthcare in the future, or for a period of time, for themselves or their families. Inducements which research ethics committees in developing countries have considered acceptable include money in the form of payments for travel, inconvenience or work lost, food, photographs or film, and healthcare for individuals and their families during research.¹⁶
- 6.26 The point at which inducements become inappropriate is not always clear. Principle 11 of the 1991 CIOMS guidelines draws attention to the fact that ‘it can be hard to draw the line between exerting pressure, or offering inappropriate inducements, and creating legitimate motivation’. However, it is possible to offer some guidance to assist attempts to draw this line. It should be remembered that without some prospect of benefit, either for themselves or others, most individuals would be unlikely to consent to participate in any research. We consider that researchers should, at the very least, aim to ensure that participants are not placed in a worse position by participating in research. The payment of reasonable expenses incurred by the participant, or remuneration for loss of earnings suffered is generally considered to be acceptable and may be necessary in developing countries where high unemployment means that participants are only able to take part in research programmes with such support.¹⁷
- 6.27 An inducement may persuade an individual to change his or her mind about entering a research project, but this in itself is not enough to make it inappropriate. For example, it may well be a rational choice not to take part in a research project, which may or may not provide any personal

15 A number of national laws and declarations, including the Helsinki Declaration make clear that potential participants in a research project should be told beforehand that they have the right to abstain from participation, or, if they do take part, to withdraw from the study at any time without reprisal. This principle was also included in the CIOMS/WHO 1993 guidance which emphasises the right of the subject to refuse to participate in the study, or withdraw from it without penalty or loss of benefit. Similar provisions have been imported into a number of the national ethical codes or laws.

16 Nuffield Council on Bioethics (1999) **The Ethics of Clinical Research in Developing Countries**, Nuffield Council on Bioethics, London: paragraph 44.

17 Principle 12 of the 1991 CIOMS guidelines states that it is acceptable to repay expenses incurred, and that promises of compensation and care in case of damage, injury or loss of income are not to be considered as inducements.

benefit, unless some extra benefit is provided. However, inducements can also change a prospective participant's mind in a less benign manner, so that their calculation of the costs and benefits of the research results in their decision that the benefit offered by the inducement outweighs all risks, however substantial. This could cause individuals to expose themselves to risks or potential harms that they would ordinarily view as unacceptable, and it is in such circumstances that the inducement would be inappropriate.¹⁸

- 6.28 The greater the inducement, the more likely it is to be inappropriate, because it may cause an individual to ignore or devalue his or her concerns about the risks involved in a research project. Special care must be taken, therefore, when research is accompanied by significant risks. The more serious the risks faced by a participant in research, the more closely the level of inducement should be scrutinised, to ensure that it is not inappropriate.
- 6.29 It is an inescapable fact that people who are ill may place great weight on a possible health benefit, even if the probability that it will occur is relatively low. This means that involvement in research which, of necessity, involves medical treatment, may amount to an inducement since the participant will receive medical treatment for his or her condition and may thus be less likely to refuse. This does not necessarily mean that the individual has been exploited. However, when participants are ill and do not have alternative ways of receiving treatment, the possibility for exploitation is greater. The CIOMS guidelines note that 'someone without access to medical care may be unduly influenced to participate in research simply to receive such care'.¹⁹
- 6.30 Guaranteed healthcare or a payment offered to individuals on condition that they take part in a research project could be considered to be exploitative if otherwise there is a very low probability of receiving such a benefit. This contrast in benefits, depending on whether an individual enrolls in research is particularly important in developing countries (see Box 6.5). Research ethics committees should bear this in mind when assessing whether it is acceptable to conduct a research projects which may involve more than minimal risk. In such circumstances special care should be taken when determining the nature of additional healthcare to be offered to participants as an inducement.

BOX 6.5 Views on the benefits of taking part in research

'How useful is the issue of informed consent in the Philippines and other developing countries, since it is always the poor in trials who cannot afford the drugs on the market? It is their only realistic form of treatment and they are not truly free to decide not to participate.'¹

'When the project first ended, the staff told me about a new project I might join and I decided to enrol again. If there were no studies, I would not have the opportunity to take anti-HIV medication.'²

'The study staff gives good advice and when this project is over I hope I can enrol in another study. For that matter, I hope there will be new studies for me to participate in all the time. If there would be no more studies, I don't know if I would have the strength to go on, as I would not know where to get drugs outside of clinical trials.'³

1 See Kenyon G (2000) Informed consent means little when drug trials are only means of treatment, **Medscape.com**, 26 September.
 2 HIV-NAT (The HIV Netherlands Australia Thailand Research Collaboration) (2000) **HIV-NAT. The HIV Netherlands Australia Thailand Research Collaboration. A model for HIV-AIDS clinical research in a developing country**, UNAIDS, Geneva: 42.
 3 HIV-NAT (The HIV Netherlands Australia Thailand Research Collaboration) (2000) **HIV-NAT. The HIV Netherlands Australia Thailand Research Collaboration. A model for HIV-AIDS clinical research in a developing country**, UNAIDS, Geneva: 41.

18 The CIOMS 1993 guidance states that payments should not be so large or provision of medical services so extensive 'as to induce prospective subjects to consent to participate ... against their better judgement'.
 19 CIOMS in collaboration with WHO (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects**: Commentary on Guideline 4.

6.31 We suggest when assessing the acceptability of inducements to participate in research in developing countries, those designing the research and research ethics committees should pay particular attention to:

- *harmfulness*: whether there are potential risks to the participants' health from taking part in the research
- *proportionality*: whether the inducement being offered is in proportion to the risks and costs to the participant involved in the research
- *vulnerability*: whether guaranteeing substantial benefits for taking part in research is more likely to constitute an undue inducement because prospective participants are especially vulnerable, for example because they have a terminal or chronic illness.

6.32 The CIOMS guidelines note that the propriety of inducements must be 'assessed in the light of the traditions of the culture'.²⁰ For example, some cultures may have a tradition of gifts or exchanges which will make some forms of inducement more appropriate than others. The majority of respondents to our public consultation noted that many decisions about which inducements are appropriate will depend on local circumstances. In such cases, local knowledge will be essential in making appropriate distinctions. One respondent commented:

The level [of compensation] would have to be determined locally e.g. what is considered an appropriate sum to cover time and inconvenience in the US (say \$50) would be equivalent to several years earning in rural Uganda.²¹

We recommend that dialogue is needed with sponsors, external and local researchers and communities to ensure that any inducements to take part in research are appropriate to the local context, especially in circumstances where the research exposes participants to a risk of harm. Decisions about appropriate levels of inducement will need to be justified to local research ethics committees.

Recording consent

6.33 As regards consent to research, many of the concerns raised by respondents to our public consultation and by those who attended our fact-finding meetings related to the process by which consent was recorded. A common observation was that consent forms often seemed to be designed to protect sponsors of research, pharmaceutical companies and researchers, rather than to provide prospective participants with appropriate information. The most common criticisms were that information and consent forms were too long and contained language that was inappropriate at best, or confusing and misleading at worst (see Box 6.6).

6.34 As we have made clear, it is the substance of the process for obtaining consent which is important, rather than the procedures used to record or document the process. Wherever research is being conducted, an appropriate and transparent procedure for obtaining genuine consent is required. A written consent form is merely evidence of what was agreed. If a prospective participant in research is given a consent form to sign, without there being an appropriate process for receiving information and then giving consent, a genuine consent to participate in research will not have been given, irrespective of whether or not a form has been signed.

20 CIOMS (1991) **International Guidelines for Ethical Review of Epidemiological Studies**, CIOMS, Geneva: Principle 11.
21 Response by Dr Dilys Morgan to the Working Party's consultation.

6.35 The purpose of a consent form is to record what has been agreed between the researcher and participant. Consequently, a consent form will not protect participants in research from possible harm, except to the extent that it discloses information which may lead to a prospective participant choosing whether to take part in the research and run a certain risk. Likewise, a consent form is neither an appropriate nor effective medium for seeking to limit legal liability for any possible harmful consequences of research.²² Questions about liability for harm arising from participation in research should be agreed by the parties involved in designing, sponsoring and conducting the research before the research begins (these questions will be governed by law in some jurisdictions). Participants in research in developing countries will need to be made aware of who will be responsible for looking after them should they suffer any harm as a result of research participation, and, unless informed, may be less likely than participants in developed countries to realise that they have avenues of redress.

6.36 In paragraphs 6.4–6.7 we discussed the information which participants need to be given before their consent to research should be sought. Various forms of guidance give detailed indications of the matters about which participants should be informed.²³ It should always be remembered that such devices as information sheets and consent forms are intended to assist the consent process. Researchers will need to refer to the relevant guidance and consider which matters are relevant to their research and to the context in which the research is to be conducted, and how to express the information they seek to convey. Forms which are long, complex and inappropriate for the cultural context in which they are being used, are likely to confuse, rather than inform, participants in research, and should not be approved by ethics research committees. Some ethics research committees, such as, for example, the committee in The Gambia prefer that all consent forms be no more than one page in length, and

BOX 6.6 Consent forms: criticisms from researchers

‘The mechanisms of obtaining informed consent in developed countries evolved in communities that are literate and generally aware of modern health practices. Researchers can therefore engage the potential subjects on the basis of pre-existing scientific knowledge and concepts. To use the forms that were designed in such circumstances to obtain informed consent in a non-literate community that operates on different concepts of health and disease, would be an exercise in self deception.’¹

‘Insistence by regulatory authorities on the use of complex consent forms devised for use in litigious Western societies is inappropriate.’²

‘Consent forms can be too long. Patients don’t understand them. It is quality not quantity that is important ...’³

‘When most of a population was illiterate, participants were very cautious, they [didn’t] know what they were signing or whether it could be used against them. Many researchers therefore considered verbal consent to be very important but did not require written consent.’⁴

- 1 Response by Professor Adetokunbo Lucas to the Working Party’s consultation.
- 2 Response by Professor Brian Greenwood to the Working Party’s consultation.
- 3 Comment made during Working Party’s Fact-finding meeting, Chennai, India, 21 January 2001.
- 4 Comment made during Working Party’s Fact-finding meeting, Madison Hotel, Washington, USA, 23 March 2001.

22 In many jurisdictions there are legal restrictions on the ability of individuals (such as researchers) and institutions (such as sponsors of research) to limit liability for injury caused by their own fault. Thus, even if a clause attempting to limit liability is included in a consent form, it may have no effect. However, participants in research who have signed such a form may believe that they have waived their rights and be less likely to pursue treatment or compensation for harm caused by research.

23 For example, Guideline 2 of the CIOMS 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects specifies 10 pieces of essential information which should be given to prospective research participants, including: the aims and methods of the research, the benefits that might reasonably be expected to result to the research participant or to others as an outcome of the research, any foreseeable risks or discomforts, the extent of the investigator’s responsibility, if any, to provide medical services to the research participant, confidentiality of participant data and arrangements for compensation for research-related injuries.

that appropriate language be used. Information sheets, which can be taken home and read, shared, translated and re-read, may be longer but still need to be written clearly.

Situations where consent forms are inappropriate

6.37 There are circumstances in which, while genuine consent to research can be obtained, it may be inappropriate to ask participants in research to sign consent forms, no matter how well designed. One obvious example is when research is being conducted in an illiterate population. The Working Party considers that it is not consistent with the duty of respect for persons to require a prospective participants to 'sign' a written consent form that they are unable to read.²⁴ Some forms of guidance explicitly recognise that written guidance will not be appropriate in all circumstances and set out appropriate safeguards.²⁵ In its recent report, the US National Bioethics Advisory Commission recommended:

US research regulations should be amended to permit ethics review committees to waive the requirements for written and signed consent documents in accordance with local cultural norms. Ethics review committees should grant such waivers only if the research protocol specifies how the researchers and others could verify that research participants have given their voluntary informed consent.²⁶

6.38 In other societies, literate participants may fear that signing forms may link them to particular organisations and leave them open to retribution from repressive regimes.²⁷ In some cultures, participants' only experience of signing forms may be in relation to tax documents or court proceedings. Thus, signing a consent form is likely to have negative connotations, making otherwise willing participants less likely to take part. In one research trial examining the consequences of domestic violence, it was considered inappropriate to ask female participants to sign a consent form before enrolling them in the research because of their concerns that signing a form would mean that a record of victims of domestic violence would be kept and this might lead to them suffering more harm.

6.39 If requesting that participants sign consent forms is inappropriate (see Box 1.1), other means of recording their genuine consent to participation in research is required to protect them from being enrolled in research that they have not consented to. In many circumstances, the research worker who is informing the participant will sign a form stating that the appropriate information was given and verbal consent received. An alternative is to record consent on audio tape. As an additional safeguard, it is desirable for an independent witness to observe the verbal consent. In some circumstances it may be more appropriate to have an independent witness to observe the process of providing information to the community and individuals, rather than observing the verbal consent to participate in research (see Box 6.7).

24 However, in such populations participants may find it useful to take written information sheets away with them for discussion with literate family members or colleagues, and for future reference.

25 For example, the Declaration of Helsinki (2000) (paragraph 22) states that where written consent cannot be obtained, verbal consent must be fully documented and witnessed. **The Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa** (2000) in referring to vulnerable communities state that where a person is illiterate 'verbal consent ... should be obtained in the presence of and countersigned by a literate witness' (paragraph 3.5).

26 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume 1 Report and Recommendations of the National Bioethics Advisory Commission**, Bethesda, Recommendation 3.11.

27 The 'Guidelines for the Conduct of Health Research involving Human Subjects in Uganda' note that a research participant's wish not to execute a written informed consent form should be honoured but the investigator must obtain oral informed consent and document such. NBAC (2001) recognises that this rejection stems from Uganda's past experience of torture and persecution of individuals found to be associated with particular enterprises and that individuals may consequently be reluctant to sign a form which associates them with certain activities.



6.40 **Information sheets and consent forms must be designed to assist participants to make informed choices. We recommend that the information provided should be accurate, concise, clear, simple, specific to the proposed research and appropriate for the social and cultural context in which it is being given. Where it is inappropriate for consent to be recorded in writing, genuine consent must be obtained verbally. The process of obtaining consent and the accompanying documentation must be approved by a research ethics committee and, where only verbal consent to research is contemplated, include consideration of an appropriate process for witnessing the consent.**

BOX 6.7 Witnessing verbal consent

Some forms of large-scale research in developing countries, such as research into vaccines, may involve many thousands of participants. In such circumstances information may be provided in a number of ways, including by television, radio and articles in newspapers. In addition, regional, local and community meetings may be held to discuss the research. If participants wish to take part in research, they will then attend one of a number of sites where the vaccine is to be administered. In such circumstances, where there is a limit to the resources and appropriately trained staff available, it may be more appropriate for the provision of information to be witnessed, rather than to attempt to provide witnesses at the field sites to confirm that each individual who attends wishes to participate in the research.

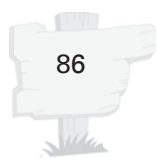
84 หน้าว่าง



Chapter 7

Standards of care

86 หน้าว่าง



Introduction

7.1 This chapter examines the ethical considerations that arise when researchers determine the standards of care to be provided for participants in research. In particular, we focus on whether participants in the control group of a research trial should be provided with a universal standard of care, regardless of where the research is conducted (see Box 7.1). This issue was highlighted in 1997 in the dispute about the standard of care to be provided to those involved in clinical trials investigating the prevention of the transmission of HIV from mother to child (see Box 1.2).

7.2 Research conducted in developing countries should be relevant to the healthcare needs of that country (see Chapter 2). However, debate has arisen about how the requirement that research be relevant should be balanced against the need to avoid exploitation of participants in research in developing countries. The debate arises in the following way. Some argue that when research is externally sponsored, participants in developing countries should receive the same standard of care and treatment as would participants in the country sponsoring the research. In contrast, others claim that the requirement that participants be offered the same standard of care and treatment, whether or not they live in developed or developing countries, would prevent some forms of research from being carried out which could lead to improved healthcare in developing countries. For example, researchers may seek to determine whether a new treatment for a disease is better than the one currently available in a developing country. To do this they may want to compare the new treatment with the current treatment that is available within that country, rather than with another, but much more expensive treatment that is available in developed countries.

BOX 7.1 Standards of care

We are aware that use of the term 'standard of care' has been criticised in the context of research related to healthcare because of its ambiguity.¹ Rather than introduce a new term, we have chosen to adopt the term 'standard of care' in the Report, and define it as: 'the nature of the care and treatment that will be provided to participants in research'.² We use the term simply as a generic description of the range of preventive or curative treatments (or lack of them) and diagnostic interventions which are made available to participants.

We use the term 'universal standard of care' to indicate the best current method of treatment available anywhere in the world for a particular disease or condition. For most diseases and conditions such a standard of care is routinely available to only a small proportion of the world's population.

1 See for example, National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**: 9 and Benatar SR and Singer PA (2000) A new look at international research ethics, **British Medical Journal**, 321 824-6.

2 While the term 'standard of care' is used in law to refer to the standard of treatment that a court would conclude that a reasonable physician would provide in the circumstances, the term is used here to describe what happens in practice, whether or not it could be considered to be reasonable or appropriate.

Existing guidance

7.3 The existing international and national guidance embraces a range of interpretations about what standard of care should be provided during the conduct of research (see Table 7.1 and Appendix 1 Table 2). The Declaration of Helsinki (2000) is the primary source of guidance on which the majority of other guidance draws. It is, therefore, our starting point. The relevant provisions are set out in Table 7.1. In the context of developing countries, the best current method of treatment (paragraph 29) is frequently not accessible and the majority of people are 'economically and medically disadvantaged' (paragraph 8). The difficulties that can arise when meeting the requirement of comparing a new treatment to the best current method of treatment while also recognising the needs of the economically and medically disadvantaged are discussed below.

Table 7.1**Primary sources of international guidance on standards of care**

Source	Text
CIOMS 'International Ethical Guidelines for Biomedical Research Involving Human Subjects' (1993)¹	Research in developing countries should be 'responsive to the health needs and the priorities of the community in which it is to be carried out'. Guideline 8 'If there is already an approved and accepted drug for the condition that a candidate drug is designed to treat, placebo for controls usually cannot be justified'. Commentary on Guideline 14
WHO 'Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products' (1995)	'The investigator is responsible for adequate and safe medical care (or dental care, where appropriate) of subjects during the trial ...' Principle 4.1 'In accordance with Sections 4.1 and 4.3 of these guidelines, the investigator must ensure the safety of the trial subjects. This includes providing the best possible care for subjects experiencing any trial-related adverse events and conducting a thorough investigation to determine causality'. Principle 7.1
International Conference on Harmonization (ICH) Harmonised Tripartite Guideline. Guideline for Good Clinical Practice (1996)	'Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)'. Principle 2.1 'During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events ... related to the trial'. Principle 4.3.2
World Medical Association 'Declaration of Helsinki' (2000)	'The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods.' Paragraph 29 'Even the best proven prophylactic, diagnostic and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.' Paragraph 6 'The particular needs of the economically and medically disadvantaged must be recognised'. Paragraph 8
UNAIDS 'Ethical Considerations in HIV Preventive Vaccine Research' (2000)	'As long as there is no known effective HIV preventive vaccine, a placebo control arm should be considered ethically acceptable in a phase III HIV preventive vaccine trial'. Guidance Point 11 'Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of ... circumstances listed.' ² Guidance Point 16

¹This guidance is currently being modified and the revised edition is expected to be published in 2002.

²Circumstances include: level of care and treatment available in the sponsor country, highest level of care available in the host country, highest level of treatment available in the host country (including the availability of antiretroviral therapy outside the research context in the host country), availability of infrastructure to provide care and treatment in the context of research, potential duration and sustainability of care and treatment for the trial participant.

Defining the best current method of treatment

- 7.4 When considering what the Helsinki Declaration requires, a clear understanding of the complexities of defining 'best current' method of treatment is needed. One definition of the best current method for a particular disease might be that which is most effective. However, achieving agreement about the most effective method is often far from straightforward. First, there may be a divergence of views within a particular medical community about what constitutes the best method of treatment. Even the evidence from controlled trials may be inconclusive or subject to debate, leaving scope for disagreement about which method of intervention is the 'best'. Secondly, even if one medical community reaches a consensus about what constitutes the best current method of treatment, there may be disagreements among different medical communities. For example, the UK and US have different views about the methods used to screen for lung cancer (see Box 7.2).
- 7.5 Although there may be some debate about what constitutes the best current method of treatment available anywhere in the world, there is usually less room for debate about which is the better

when comparing the methods available in developing countries as against developed countries. Because of the greater resources available, in many instances it will be unarguable that the care available in developed countries for a particular condition is better, i.e. more effective, than that widely available in a developing country. In light of this disparity, the issue we address is what standard of care should be provided to participants in research when there is a discrepancy in the standard of care in the country in which the research is conducted and the country sponsoring the research.

BOX 7.2 Screening for lung cancer

At present a trial is being planned in the UK and other European countries to determine whether a novel form of screening for lung cancer will reduce mortality by detecting the cancer. In the trial, one group will receive the new form of screening (low dose spiral computed tomography), while the control group will receive no screening. In a similar trial planned in the US, this new form of screening will be compared to screening using a chest x-ray. In contrast to the US, the view held in the UK, and in some other European countries, is that there is no evidence that a chest x-ray is an effective method of screening.

The appropriate standard of care for control groups in clinical trials

7.6 The different approaches that have been proposed when deciding the level of care that should be provided for those in the control group of a clinical trial can be divided into two broad categories:

- universal: the best treatment available anywhere in the world, wherever the research is conducted
- non-universal: the treatment available in a defined region.

Our aim in making this distinction is to separate the universal or global 'best' from all other levels of care, be they local, regional or national.

7.7 The approach of those who are in favour of a universal standard of care being provided to the control group in clinical trials is set out in a widely quoted editorial by Marcia Angell in the **New England Journal of Medicine**:

I believe that our ethical standards should not depend on where the research is performed ... Furthermore I believe the nature of investigators' responsibility for the welfare of their subjects should not be influenced by the political and economic conditions of the region. It would follow that these conditions should not be used to justify providing a lower standard of care for some subjects than they would have received had they taken part in the same study in a different place. In practical terms any other position could lead to the exploitation of people in developing countries, in order to conduct research that could not be performed in the sponsoring countries.¹

7.8 Marcia Angell sets out at least three principles: one concerned with the importance of avoiding the exploitation of people in developing countries; one concerned with the responsibilities of researchers and sponsors or research; and one concerned with the need to avoid making the standard of care depend upon the local context. We address each of these in turn.

1 Angell M (2000) Investigators' responsibilities for human subjects in developing countries, **New England Journal of Medicine**, 342(13) 967-9.

Avoiding exploitation

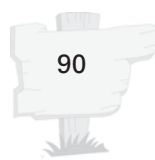
- 7.9 The Working Party is firmly of the view that the need to avoid exploitation is imperative. As we have stated in Chapter 4, it is a fundamental ethical principle that those involved in research in developing countries, including research teams, pharmaceutical companies and governments, should not take advantage of the vulnerabilities created by poverty or a lack of infrastructure and resources. However, as discussed below, the Working Party considers that insisting upon a universal standard of care may not always be the best way to respect this principle.
- 7.10 At first sight, justice might seem to require that we treat people identically, regardless of context, because justice demands equal respect. If showing respect for the participants in a particular research project in the developed world demands that they receive a particular intervention, it would seem to follow that parity of respect means that participants in similar research conducted in the developing world should receive the same intervention. To apply a lower standard of care would thus be not only to take advantage of the participants' vulnerabilities, but also to commit an additional wrong by perpetuating an injustice. However, the principle of equal respect does not imply that we must behave towards others in a uniform manner, since features of individuals and of their circumstances will differ. Parity of respect requires us to address the specific needs and circumstances of individuals in determining how to behave towards them. What we mean by equality is not that people must always be treated identically, but that 'for every difference in the way men are treated, a [relevant] reason should be given'.² Thus, the context of the research in different countries must be critically assessed to establish whether or not it provides a morally relevant reason for offering a different standard of care (see paragraphs 7.17–7.18).

Responsibilities of researchers and sponsors

- 7.11 The goal of research related to healthcare is to gain information about diseases and to discover better methods of prevention, diagnosis and therapy that can be applied to benefit the wider community. Raising the quality of healthcare available to those in developing countries to the standard that exists in developed countries is necessarily a long-term goal. Given current inequities, it will clearly not be possible, in the short term, to improve the health of their populations to the level of their counterparts in the developed world. Research on improving preventive and therapeutic methods in developing countries is necessarily conducted within this context.
- 7.12 Some commentators have argued that by failing to extend to those participating in research in a developing country, the level of treatment that would be given in the sponsors' own, more wealthy country, external sponsors thereby harm the participants in research. Indeed, a central argument against the perinatal HIV-transmission trial (see Box 1.2) put forward by Lurie and Wolfe was that the conduct of the research would 'lead to hundreds of preventable HIV infections in infants'.³ One response to this argument is to suggest that in not providing a universal standard of care, research sponsors do not harm the participants, they merely fail to benefit them; that is, they do not put participants in a worse position, but neither do they improve their position. However, this cannot be the end of the matter.
- 7.13 The fundamental duty to alleviate suffering has a natural extension, namely a duty to provide a positive benefit, though defining the extent of the duty to benefit in a given situation is a

2 See Williams B (1973) *The Idea of Equality*, in Williams B **Problems of the Self**. Cambridge University Press, New York, for a clear exposition of the view that what we mean by equality is not that people must always be treated identically, but that 'for every difference in the way men are treated, a reason should be given' that is relevant.

3 Lurie P and Wolfe SM (1997) Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. **New England Journal of Medicine**, 337: 853–6.



challenging task.⁴ In many research projects, it will be the case that the greater wealth of the sponsoring country or institution means that there will not be a financial barrier to offering a higher level of care than that which is available locally to those in a specific research study. The Working Party notes that a person's duty to benefit another is related to his or her capacity to do so, whether financial or practical. If a particular benefit cannot be provided for reasons of practical constraint, the duty to do so is weakened. Conversely, if a country's wealth allows it to confer a benefit on the inhabitants of another country when that country cannot do so itself, the wealthier country has a stronger duty to provide that benefit.

- 7.14 In some research projects, the care provided to participants in developing countries can be higher than the national standard without significantly affecting the requirement to conduct research relevant to that country's health needs or the economic constraints on sponsors. This is most likely to be the case with respect to the treatment of conditions that arise among participants in research during the course of a study. For example, consider a trial of a new vaccine for malaria that is conducted in an area where there are high levels of drug-resistance to the disease. The main aim of the research may be a comparison of the incidence of malaria in the two arms of the trial (new vaccine and control), but researchers may be able to make available medicines that may not be available nationally for the treatment of cases of malaria. However, the desirability and sustainability of such measures should be fully discussed with local health services in advance, to ensure that the otherwise unavailable treatment does not lapse as soon as the research is completed (see Chapter 9).
- 7.15 It must be noted, nonetheless, that the most effective way to discharge the duty to alleviate suffering with respect to a particular research participant will not necessarily be to provide them with a universal standard of care during the conduct of research. For example, patients with chronic diseases may not be better off in the long term if they receive a standard of care during a research project which cannot be sustained once the project ends. In other words, the question of what standard of care and treatment should be made available during the conduct of research may not be separable from the question of what care is made available once the research is completed. Should participants require long-term care, the two issues necessarily overlap.

Unsafe practices

- 7.16 Researchers will be obliged to raise the standard of care above the national standard when that national standard is unsafe. In the example from South-East Asia set out in Box 7.3, the re-use of equipment for taking blood was the routine local practice. Researchers have a duty to prevent avoidable harm to participants in research. The use of unsafe or harmful practices, even if they

BOX 7.3 Research in South-East Asia

Research studies in one South-East Asian country required a lancet to be used to take a blood sample. In that country it was common practice for lancets to be re-used after being dipped in alcohol. In most countries, lancets are not re-used because of the high risk of cross-infection. Health professionals in the country were aware of the risks inherent in the multiple use of lancets, but a period of famine had just ended and there were very limited financial resources to purchase new equipment. Researchers wanted disposable lancets to be used in the study. To avoid creating internal difficulties within the hospital, it was therefore necessary to provide an adequate supply of such lancets for the whole of the hospital.¹

1 Personal communication, Working Party fact-finding meeting.

4 For a thought-provoking attempt to set out the limits of this obligation, see Unger P (1996) **Living High & Letting Die: our illusion of innocence**, Oxford University Press, New York.

are routine locally, is unacceptable. It follows that adopting a non-universal rather than a universal standard of care in research does not provide a justification for employing unsafe practices.

The importance of the research context

7.17 In paragraph 7.10 we noted that equal respect for participants in research does not necessarily entail that they should receive equal treatment, regardless of where the research may be conducted. Instead, the circumstances in which the research will be conducted must be critically assessed to establish whether or not the variations in circumstances provide a morally relevant reason for offering a different standard of care.

7.18 We take the view that, in determining the appropriate standard of care to be provided to participants in the control group of a research trial, a number of factors should be considered by sponsors, researchers, and research ethics committees. These include:

- the appropriate research design(s) to answer the research question; (in some situations only one research design may be appropriate to answer the research question, in others a number of research designs, in which different standards of care are offered to the control group, may be possible)
- the seriousness of the disease and the effect of proven treatments
- the existence of a universal standard of care for the disease or condition in question and the quality of the supporting evidence
- the standard(s) of care in the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can be afforded by the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can effectively be delivered in the host country(ies) during research
- the standard(s) of care which can be provided in the host country(ies) on a sustainable basis.

BOX 7.4 Treatment of schistosomiasis with praziquantel

For some diseases there is widespread agreement about the standard of care that will be provided for those infected, wherever they are in the world. For example, cost-effective control tools, based on treatment with praziquantel, are available for treating schistosomiasis. This has resulted in prolonged, sustainable national control programmes in endemic countries such as Brazil, China, the Philippines and Egypt, and eradication or near eradication of the disease in countries such as Puerto Rico, Venezuela, Saudi Arabia, Tunisia and Morocco. Africa now accounts for an estimated 80% of the remaining cases of the disease and WHO is committed to reviving control of the disease in Africa, with a simple morbidity control package including affordable access to praziquantel at all levels of healthcare.¹

¹ See <http://www.who.int/ctd/schisto/index.html>.

7.19 Taking the above considerations into account, in some circumstances, it will be clear that a control group in a clinical trial should receive a universal standard of care, wherever they live (see Box 7.4). For example, if research were to be conducted in any developing country into a new treatment for schistosomiasis, we consider that the control group in such research should at least be offered praziquantel or a medicine with the same efficacy. We base this view on the fact that an effective, proven treatment for schistosomiasis exists and has been approved and implemented in affected countries around the world. The treatment has been demonstrated to be affordable and feasible to deliver, in a sustained manner in developing countries. Any future research is likely to focus on forms of care that are better than this treatment, and thus it will be an appropriate comparison for the control group to receive.

- 7.20 In contrast to the case above, there are situations in which it is clear than even if there were an agreed universal standard of care for a disease, it may not be possible for this standard to be provided to the control group in a research project. In some cases the universal standard of care will not be able to be provided because of practical considerations. For example, if a treatment was sought for a condition such as liver cancer (which often develops in carriers of hepatitis), the universal standard of care includes surgery to remove the tumour or a liver transplant. While the sophisticated infrastructure required to provide such treatments is available in developed countries, (including intensive care units, trained surgeons and healthcare staff) it is very limited or absent in the majority of developing countries. If researchers sought to develop a form of treatment for liver cancer which would be affordable, deliverable and sustainable in developing countries, it is unlikely that it would be possible to provide a universal standard of care to the control group in the research.
- 7.21 Practical constraints may not be the only factor preventing delivery of a universal standard of care in research. For example, when research into preventing the perinatal transmission of HIV was conducted in the Cote d'Ivoire in 1995, researchers were not able to provide women in the control group with the universal standard of care which involved administration of the medication in pregnancy, intravenous infusion during labour and delivery, and administration of the medicine to the infant four times a day for six weeks. This complicated regimen, which requires voluntary counselling and testing for HIV to be performed early in pregnancy, has limited application for many developing countries where women have poor access to antenatal care and may only seek assistance from healthcare workers after the onset of labour.
- 7.22 In the two cases outlined above, even though a universal standard of care cannot be provided to participants, it can be convincingly argued that the research should nevertheless be conducted because it offers the opportunity of developing responses to important healthcare needs in developing countries.
- 7.23 We have set out contrasting cases in which it can be said to be respectively appropriate or inappropriate, to offer a universal standard of care to participants who are in control groups. However, the decision about whether or not a universal standard of care is called for is usually not so straightforward. It involves a careful consideration of the various factors outlined in paragraph 7.18. In circumstances where it is apparent that a universal standard of care is not appropriate, further analysis of these factors will be required to determine what the appropriate standard of care should be.
- 7.24 In some circumstances, differing research designs may each provide relevant information about a particular disease or intervention. Researchers and research ethics committees will need, therefore, to consider which design is the most suitable. A number of respondents to our public consultation and in our fact-finding meetings stressed the importance of involving local researchers when designing research and determining appropriate standards of care. An awareness of the standards of care currently being used within developing country(ies) and of information sought by local providers of healthcare will increase the likelihood of research being relevant to local needs and producing results that are likely to be applicable in developing countries.
- 7.25 It should be borne in mind that any definition of the 'best treatment' which may be available in a country is subject to change over time, in response to the results of research, and will affect the standard of care that it is appropriate to offer to participants in research. For example, in initial trials investigating perinatal HIV transmission in Thailand which involved testing a short course of therapy (see Box 1.2), a trial design in which the control group received a placebo was considered to be acceptable. Since this research has demonstrated the effectiveness and feasibility of the short course treatment in Thailand, further research which provides the control

group in the research project with anything less than the short course of treatment would be unethical. Currently, trials to assess the potential additional efficacy of new medicines or combinations of medicines in preventing perinatal transmission of HIV in a developing country setting provide a short course regimen of proven efficacy to the control group.⁵

Defining a non-universal standard of care

- 7.26 Where it is not appropriate to require that a universal standard of care be provided to the control group, in the light of all the relevant circumstances, questions arise about what standard of care should be provided. For example, should it be a national, regional or local standard? Should it be the level of care available in a local hospital, a district hospital, tertiary institution or within the private sector? The ultimate goal of research must be to provide information about treatment and other interventions which can then be used by national governments to ensure that improvements are made in the provision of healthcare. Thus, for policy reasons, it seems sensible to take the particular country as the unit of focus, as it is national governments which, by and large, take responsibility for the health of their citizens and which make decisions about the provision of healthcare. With knowledge of the resources available to them, governments make decisions about the level of care which they can provide for the prevention and treatment of specific diseases or conditions. In that context, they set targets for the level of care that they will strive to achieve, often recognising that it will not be possible to meet this goal.
- 7.27 The Working Party is of the view that in externally-sponsored research, the level of care that ought to be offered to participants should, as a minimum, be the standard that the country endeavours to provide nationally. In many circumstances, it may be appropriate for researchers to offer a higher level of care than this, while still conducting research that is relevant to the local setting. Exceptionally, it may be appropriate to provide a level of care that falls below the national standard. The ethical justification for this, however, will need to be carefully argued and accepted by local authorities and ethical review bodies before such research can be conducted (see paragraph 7.30).
- 7.28 We have previously noted that defining the 'best treatment' is not straightforward (see paragraphs 7.4–7.5, 7.25). Similarly, it may not be easy to identify a single 'national standard' of care. In many countries, the 'best' levels of care may be available within private healthcare systems, although in most developing countries these provide care for only a small proportion of the population, while most people are served by the public health service. In setting the national standard of care, it would seem appropriate to concentrate on what can be provided within the public health system, as this is under the direct control of national governments. The challenge in defining the national standard of care may be greater in large countries (with regional differences in access to healthcare) than in small countries. In some circumstances it may be appropriate to use a regional standard (within a country) rather than the national standard. However, again this will need to be carefully justified.
- 7.29 We conclude that discussion with clinicians, researchers and representatives of government and health authorities within the host country is essential so as to establish what the best national level of treatment available as part of the national public health system is. **We recommend that in setting the standard of care for the control group of a particular research project the context in which the research is to be conducted be carefully evaluated. A suitable standard of care can only be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a**

5 For example a study in South Africa is comparing the efficacy of two new medicines alone, and in combination with a zidovudine only short course regimen.

universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered to the control group is the best intervention available for that disease as part of the national public health system. A summary of the reasoning behind this conclusion is given in the Box 7.5.

Deviations from the national standard

- 7.30 In exceptional circumstances, research may be proposed which involves the use of a standard of care that is lower than the best available intervention as part of the host country's public health system for the disease being studied. For example, researchers may wish to demonstrate that what is deemed to be the best treatment available through the host country's public health system is ineffective, or even harmful, by comparing it to a placebo, or an apparently lesser standard of care. Alternatively, researchers may wish to show that the best available intervention in the host country as part of the public health system for a particular disease is so beneficial that it should be made more widely available within the country (see Box 7.6). Prophylactic chemotherapy to prevent tuberculosis (TB) is widely recognised to be the best treatment for individuals who are HIV positive in countries in which TB is endemic. However, it is not possible to provide this treatment in many African countries that can barely maintain their current TB Control Programmes. Research to investigate how to implement prophylaxis for TB might compare current practice (normally no prophylaxis) with other approaches. If an aim of research into healthcare is to improve current forms of treatment, then there may be circumstances in which it is justified to compare current local practice with a new treatment, in the local setting.

BOX 7.5 Summary of arguments about standards of care

The principle of not exploiting those who are vulnerable lends support to the adoption of a universal standard of care so that people in different countries receive the same care and treatment during research.

However, in some circumstances it may not be possible to adopt a universal standard of care. In other circumstances, providing a universal standard of care to the control group may not provide research results that are relevant to the country in which the research is conducted.

In an ideal world, variations in healthcare resources throughout the world would be eliminated. But the duty to undertake research requires us to act even in a non-ideal world where resources are limited and not equally distributed.

Therefore, the challenge is to fulfil this duty to undertake research in a way that is consistent with the principle of not exploiting those who are vulnerable.

This can be achieved by requiring the standard of care to be universal where possible, or at least that which is available as part of the national public health system of a country, and by improving standards wherever feasible.

BOX 7.6 STD and HIV research

In one country, a national programme for the treatment of sexually transmitted diseases (STDs) was not widely implemented, so that, in many regions, the availability of antibiotics to treat STDs, as contemplated in the programme, was limited. Research was conducted in which randomised communities received either existing care, or the antibiotic treatment for STDs recommended in the national programme. The rationale for this research was to demonstrate that if the national programme was widely available, it would reduce both the level of infection with STDs and HIV. Once this finding was demonstrated, the evidence that treating STDs would also reduce the level of HIV infection provided an incentive for the government to make the national programme for treating STDs widely available. The research also demonstrated that it was possible to implement the national programme on a large scale.¹

¹ Grosskurth H, Moshia F, Todd J, Mwijarubi E, Klokké A, Serkoo K *et al.* (1995) Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial, **The Lancet** 346(8974) 530–6.

- 7.31 Research on the management of outbreaks of disease in isolated places may necessarily involve standards of care that are lower than the best which are available nationally. For instance, research on the management of an outbreak of meningococcal meningitis in Northern Nigeria may have to accommodate thousands of people being cared for in the open, the performance of lumbar punctures and the administration of single-dose antibiotic therapy under conditions that are clearly less than the national standard. Denying these communities the opportunity to participate in research denies them improvements in healthcare and new ways to manage sick patients in settings with very limited resources.

Research into preventive measures

- 7.32 In some forms of research, such as those designed to determine the incidence of a disease in a population, or to prevent participants from contracting or developing a disease, the standard of care received by participants who develop the disease will not be immediately relevant to the research.⁶ This is because the research is focused on preventing participants from contracting the disease, rather than the subsequent effects of and possible treatments for the disease. Under these circumstances, however, there is still a need to consider the standard of care which a patient should receive because the disease, once diagnosed, may have serious implications for the individual. The issue was the subject of extensive consultation in the developing countries in which the research to develop a vaccine to prevent infection with HIV was to be undertaken. Following these consultations the UNAIDS guidance on ethical considerations in research on a HIV preventive vaccine recommends:

Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of the circumstances listed below. A comprehensive care package should be agreed upon through a host/community/sponsor dialogue, which reaches consensus prior to initiation of a trial, taking into consideration the following:

- Level of care and treatment available in the sponsor country
- Highest level of care available in the host country
- Highest level of treatment available in the host country, including the availability of antiretroviral therapy outside the research context in the host country
- Availability of infrastructure to provide care and treatment in the context of research
- Potential duration and sustainability of care and treatment for the trial participant.

Guidance Point 16⁷

- 7.33 **We endorse Guidance Point 16 of the UNAIDS guidance on Ethical Considerations in HIV Preventive Vaccine Research. We conclude that when research into preventive measures is conducted, wherever appropriate, participants who develop the disease being studied should be offered a universal standard of care for the disease under study. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered is the best available intervention as part of the national public health system for that disease.**

6 For example, in vaccine trials and studies of other measures to prevent diseases such as malaria and AIDS, research will be designed to test the effectiveness of the proposed intervention. This assessment can be made by determining how many of those who receive the intervention go on to develop the disease being studied.

7 UNAIDS (2000) **Ethical Considerations in HIV Preventive Vaccine Research. UNAIDS Guidance Document: Guidance Point 16.**

Care for other conditions

- 7.34 During research into some diseases, participants may develop a condition that is related to the condition under study. For example, in certain regions individuals with STDs are more likely to become infected with HIV than those without (see Box 7.6). In addition, during research, participants may develop an entirely unrelated condition. In some circumstances, it may be relatively easy for researchers to treat the condition or refer participants to a local health centre where treatment can be provided. In other cases, researchers may not have the expertise to treat the condition effectively and appropriate treatment may not be available locally as part of the public health system.
- 7.35 As discussed in paragraph 7.13, in addition to researchers' duty not to harm participants in research, there is a duty to benefit participants where possible. Thus, where it is feasible for researchers to diagnose and treat an illness which arises, or to ensure that effective treatment is available at a local level, they have a duty to do so. This is a complex issue and decisions will need to be made on a case-by-case basis following discussion with clinicians, researchers and representatives of government and health authorities within the host country. **We recommend that before research begins, agreement should be reached about the standard of care that should be provided to participants in research who already have or who develop diseases other than the disease being studied. We conclude that the minimum standard of care that should be offered is the best intervention available as part of the national public health system. Any proposal which contemplates care of a lower standard deviation must be justified to the relevant research ethics committees.**

98 หน้าว่าง



Chapter 8

Ethical review of research

100 หน้าว่าง



Introduction

8.1 The requirement that the ethics of proposed research be reviewed (hereafter called ethical review) is designed to protect participants in research. The need for such review is now widely recognised and set out in national and international guidance (Table 8.1 and Appendix 1 Table 4). The research ethics committees which typically undertake such reviews are a relatively recent

Table 8.1

Primary sources of international guidance on reviewing the ethics of research

Guidance	Text
Council for International Organizations of Medical Sciences (CIOMS) 'International Guidelines for Ethical Review of Epidemiological Studies' (1991)	'The requirement that proposals for epidemiological studies be submitted to independent ethical review applies irrespective of the source of the proposals... Sponsors should recognize the necessity of ethical review and facilitate the establishment of ethical review committees. Sponsors and investigators are expected to submit their proposals to ethical review, and this should not be overlooked even when sponsors have legal power to permit investigators access to data. An exception is justified when epidemiologists must investigate outbreaks of acute communicable diseases... Nevertheless, in such circumstances the investigator will... respect the rights of individuals'. Principle 33
CIOMS 'International Ethical Guidelines for Biomedical Research Involving Human Subjects' (1993)	'All proposals to conduct research involving human subjects must be submitted for review and approval to one or more independent ethical and scientific review committees. The investigator must obtain such approval of the proposal to conduct research before the research is begun'. The function of ethical review to protect participants whilst ensuring the quality of research is also elaborated: 'Scientific review and ethical review cannot be clearly separated: scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risk or inconvenience to no purpose'. Guideline 14
World Health Organization (WHO) 'Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products' (1995)	'The protocol, appendices and other relevant documentation should be reviewed from a scientific and ethical standpoint by one or more (if required by local laws and regulations), review bodies... constituted appropriately for this purpose and independent of the investigator(s) and sponsor'. Paragraph 2 'The investigator, or the investigator and the sponsor, must consult the relevant ethics committee(s) regarding the suitability of a proposed clinical trial protocol... and of the methods and materials to be used in obtaining and documenting the informed consent of the subjects... Subjects must not be entered into the trial until the relevant ethics committee(s) has issued its favourable opinion on the procedures'. Paragraph 3.2 'Prior to its commencement, the investigator must ensure that the proposed clinical trial has been reviewed and accepted in writing by the relevant independent ethics committee(s)'. Paragraph 4.9
International Conference on Harmonization (ICH) 'Harmonised Tripartite Guideline. Guideline for Good Clinical Practice' (1996)	'A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion'. Paragraph 2.6
World Medical Association 'Declaration of Helsinki' (2000)	'The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval, to a specially appointed ethical review committee...' Paragraph 13
UNAIDS 'Ethical Considerations in HIV Preventive Vaccine Research' (2000)	'HIV preventive vaccine trials should only be carried out in countries and communities that have the capacity to conduct appropriate independent and competent scientific and ethical review'. Guidance Point 6
WHO 'Operational Guidelines for Ethics Committees that Review Biomedical Research' (2000)	'Countries, institutions, and communities should strive to develop Ethics Committees and ethical review systems that ensure the broadest possible coverage of protection for potential research participants and contribute to the highest attainable quality in the science and ethics of biomedical research. States should promote, as appropriate, the establishment of research ethics committees that are independent, multidisciplinary, multi-sectoral, and pluralistic in nature. Research ethics committees require administrative and financial support'. Paragraph 3

innovation (for example, the first committee in the UK was established in 1966).¹ Committees with responsibility for reviewing the ethics of research now exist in most countries.

Levels of assessment

8.2 The Working Party considers that each proposal for externally-sponsored research in developing countries should receive three levels of assessment:

- relevance to priorities in healthcare within the country(ies)
- scientific validity
- ethical acceptability.

In this chapter, we briefly discuss assessment of the relevance of the research to priorities in healthcare and the scientific review of research, and then focus on ethical review of research. A list of questions that may be relevant during these three forms of review is set out in Appendix 3.

Relevance to priorities in healthcare

8.3 Research ethics committees are not constituted to take policy decisions on, for example, whether the findings of a research project could be implemented in the country. We consider that they should, however, determine if the implications of the possible research results have been considered, including the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful (see paragraphs 9.32–36). In addition they should request justification for research that does not include provisions for the development of expertise in research within the developing country (see paragraphs 9.50–52).

Scientific review

8.4 Rigorous scientific evaluation of each research protocol is essential. Research which is not appropriately designed will fail to provide answers to the question posed by the research, and thus have limited benefit or no benefit either to the participants, or to the wider community. Some sponsors of research conduct their own scientific review of proposed research. However, these internal reviews cannot always be relied upon. Sponsors are often presented with proposals in outline from applicants that exclude many of the details essential to scientific review, such as the size of the sample of population and the specific definition of the study groups. Internal scientific reviews of proposed research undertaken by the pharmaceutical industry may be fully or partially confidential and therefore not comprehensively available to external review committees. Research ethics committees must be satisfied that appropriate scientific review of research has taken place.

8.5 There are concerns that, in a single ethics committee, the distinction between the review of the science and the ethics, which have quite different purposes, may be ill defined. We accept that it is not possible to entirely separate the processes of reviewing the science and the ethics of a research proposal. One depends to a degree on an appreciation of issues addressed by the other. Nevertheless, they should be undertaken as separate exercises. We conclude, therefore, that these two forms of review should, where possible, be kept separate. This may, but will not necessarily, require the establishment of separate committees.

1 Ferguson P (2001) Do researchers feel an LREC hinders research? *Bulletin of Medical Ethics*, 165 17–19.

Ethical review of research

- 8.6 An ethics committee's primary task is to review the ethical acceptability of research proposals. Particular attention is usually paid to:
- the *predictable* risks involved in conducting the research
 - the anticipated benefits for the participants in research and communities to which the research will be relevant
 - the provisions within the design of the research relating to the care and protection of participants in research, including the treatment of any participant harmed by the research
 - the procedures for recruitment and selection of participants in research (including details of the group to be investigated)
 - the processes for obtaining genuine consent and provision for refusing consent or withdrawing it during research (including the adequacy of information given to participants and the acceptability of any inducements)
 - the provisions for protecting the security and confidentiality of data about patients.
- 8.7 In the preceding chapters and the following chapter, we have examined in detail a number of issues that need to be considered by research ethics committees when reviewing externally-sponsored research. These include the appropriateness of procedures for giving information about the research to prospective communities. For example, in Chapters 6 we noted that it was necessary to draw on the expertise of a local research ethics committee to ensure that procedures for consent enabled prospective participants in any research to give genuine consent, and that any inducements to participate were appropriate (see paragraphs 6.32, 6.40). In Chapter 7 we recommended that, rather than requiring that a universal standard of care should always be provided to a control group during a clinical trial, a decision should be made in each case on what would be the most appropriate level of care to be provided. Such decisions can only be made in consultation with local researchers and local research ethics committees (see paragraphs 7.18, 7.29) and should be made by reference to the reasons and argument we set out in Chapter 7. In Chapter 9 we endorse the US National Bioethics Advisory Committee (NBAC) recommendation that researchers should have to justify the lack of arrangements for securing post-trial access for effective interventions for participants in a trial to the ethics review committee (see paragraph 9.31). We also conclude that an ethics review committee would need to be persuaded of the need to carry out a study involving a novel intervention to treat chronic disease in a locality where the availability of long-term treatment is unlikely.
- 8.8 The mere presence of a research ethics committee in a country is not enough to ensure that research will be adequately reviewed. Committees may be ineffective for a variety of reasons, including a lack of financial and human resources, and a lack of training in, and experience with, reviewing the ethics of research. In Box 8.1 the current capacity of a selection of countries to conduct such reviews is outlined.

Requirements for effective ethical review of research

- 8.9 As we have said, an effective system of ethical review is a crucial safeguard for participants in research. Research ethics committees are one component of a system for ensuring the protection of participants in research within a country. However, if there is little support for a system of ethical review amongst government officials, senior members of universities and research

BOX 8.1 Differing capacities to conduct ethical review

In some developing countries there are no research ethics committees. For example, Myanmar and Laos have no formal internal ethical review process for research related to healthcare.¹ Such countries may, however, have other mechanisms in place to provide a review of research, including the possibility of review by officials from the national Ministry of Health. In addition, a country without a committee may request a research ethics committee from neighbouring countries to review proposed research. For example, in Guinea Bissau, once the government has considered proposed research and decided that it is relevant, it is passed to the national ethics committee in The Gambia, for review.

In India, there are clear and robust guidelines for externally-sponsored research, as well as for nationally funded research (see Appendix 1 Table 1). In addition to the national research ethics committee, there are many local and institutional review committees.² The quality of assessment, however, varies among the local committees.³

In Latin American countries, regulatory procedures for the evaluation of new medicinal products generally require both local scientific approval, and approval by an independent ethics committee. In Argentina, a single ethics review committee can approve multi-centre studies for centres which do not have their own ethics review committee. In Brazil, the number of research projects which have been approved has grown from 30 in 1995 to 430 in 1999, and national regulation for the ethical review of research proposals has recently been established.⁴ A federal resolution was approved in October 1996 by the National Council of Health, requiring that all research projects involving human participants receive ethical review.⁵

Research ethics procedures in Central and Eastern Europe vary greatly from one country to another, for largely historical reasons. Bulgaria, Hungary, Poland and Romania have national ethics committees as well as local ethics committees in hospitals. Albania and Lithuania have national ethics committees, while Estonia has two research ethics committees, in addition to a bioethics council and an ethics committee related to the planned Estonian Genome Project. The Czech Republic has institutional ethics committees while Russia has a committee in the Ministry of Health and another in the Academy of Medical Science: both are currently developing guidelines but are not yet reviewing research proposals. There is also a regional research committee in St. Petersburg. The Ukraine until recently has had no research ethics review system, and preparatory work here and in other Eastern European countries is supported by the Council of Europe.⁶

- 1 White N (2000) Personal communication, Wellcome – Mahidol University – Oxford Tropical Medicine Research Programme.
- 2 The ethical guidelines and the National Research Ethics Committee are the responsibility of the Indian Council of Medical Research, which had a budget of nearly US\$50 million in 1999–2000.
- 3 Personal communication, Working Party fact-finding meeting.
- 4 Brasil, Decreto 98 830, 15 Janeiro 1990 (Coleta por estrangeiros de dados e materiais científicos no Brasil).
- 5 The resolution sets out the terms of reference for the establishment and operation of ethics review boards and the creation of the Central Committee of Ethics in Clinical Research (CONEP) as an adjunct to the Ministry of Health. Research ethics committees must report to CONEP on a quarterly basis about the status of trials of new products.
- 6 Coker R and McKee M (2001) Ethical approval for health research in central and eastern Europe: an international survey. *Clinical Medicine*, 1(3) 197–9.

institutions, or local researchers, then research committees may not be established, or may be unable to function effectively due to a lack of training and resources, or a lack of independence. In some instances, researchers may submit research for approval in developing countries, only to have it ‘approved’ within a few days, with no amendments or changes proposed.² Under these circumstances concerns have been expressed that officials in developing countries do not recognise the need for effective ethical review and consider it to be simply a formality. Alternatively, the decisions of the research ethics committees may be ignored or overridden by government officials.

8.10 Furthermore, if a committee has limited independence and no clear framework of guidance to work within, there is a danger that they may take *ad hoc* rather than principled decisions, and

2 Melody Lin (2001) Personal communication, Office for Human Research Protections, US.



that these *ad hoc* decisions may reflect members' affiliations and interests, and pressure from host and foreign researchers, sponsors and local government or other administrative authorities. For example, a research ethics committee might find it difficult to refuse research that it considered inappropriate but which would bring a substantial funding to an institution or region. As we have said in paragraphs 5.25 and 5.28, the guidance on research related to healthcare can be ambiguous and difficult to apply in specific circumstances. For this reason we encourage countries to create national guidance for the clear and unambiguous application of existing international and national guidance. The need to provide training for members of research ethics committees so that they can act effectively is discussed below (paragraphs 8.26–8.29).

- 8.11 The membership of research ethics committees requires careful consideration. The aim must be to achieve an independent, multi-disciplinary, efficient committee with sufficient expertise. Recent guidance from international bodies on the membership of research ethics committees is set out in Appendix 1 Table 4. With regard to attendance, in order to ensure that meetings are quorate, it is helpful to have more members than are required for a quorum. In the case of renewal of the membership, it is helpful to maintain a rotation of new members, not least because they inevitably take time to learn about the process of ethical review. We note that the inclusion of representatives of relevant religions may present difficulties if there are several religions represented within the host community. However, many theological scholars have given substantial thought to issues that need to be considered by ethics committees and their participation may be particularly valuable.
- 8.12 In some countries, it is considered an advantage to have a majority of members in a research ethics committee who are not professionals in the various fields covered by research (sometimes referred to as lay members).³ Their primary role is to reflect the values of the local communities and the local and national culture. Particular care will need to be taken to ensure that the interests of women and members of vulnerable populations are properly taken account of by research ethics committees. In countries which do not have research ethics committees, members of a committee from a neighbouring or sponsoring country may well have an incomplete understanding of the local conditions in the host country. As a consequence, any review may be inadequate. Moreover the geographical and social isolation from the communities under study may make any monitoring of the research difficult.
- 8.13 The independence of members of ethics committees is a common problem. In many developing countries, members of research ethics committees may not be able to afford to provide the necessary time and expertise to review research at no cost. Failure to provide appropriate remuneration may contribute to delay or to inadequate reviews. However, when committee members receive a fee for review, their independence may be compromised.
- 8.14 In many developing countries, there is often a limited number of people available who have the expertise and the time and who are able to bring to bear the kind of knowledge and care required to act as effective members of a research ethics committee. One example cited to the Working Party concerned the directors of two institutes who were members of each other's ethics committees, leading to a possible conflict of interest.⁴ Moreover, prospective reviewers with the appropriate scientific background may in fact be involved in the research, creating a potential conflict of interest. Where conflicts of interest are unavoidable, the procedures for managing them should be transparent, and may include the requirement that the conflict be declared and that a member be excluded from discussions when appropriate.

3 Lay members are individuals who represent a range of community and cultural values (and are not members of the specialist professions represented on research ethics committees, such as physicians, scientists, nurses and ethicists).

4 Das PK (2000) Personal communication, Vector Control Research Centre (VCRC), India.

- 8.15 Some research ethics committees meet infrequently, or at irregular intervals, which will delay review of research protocols. For example, if a committee meets only three or four times a year, a backlog of research proposals may build up. In some situations, sufficient funding will allow research ethics committees to meet more regularly, while in others, delays caused by a lack of infrastructure, for example difficulties of travel, may be more difficult to overcome.
- 8.16 **We recommend that all developing countries should have in place a properly constituted and functioning system for the independent ethical review of research. This will include the establishment of effective research ethics committees.** Developing countries may determine that the most appropriate means of reviewing externally-sponsored research is via an independent national research ethics committee. **In such circumstances the establishment, funding and proper operation of independent national research ethics committees should be the responsibility of national governments. No research should be conducted without review at the national or local level.**

Meeting the costs of research ethics committees

- 8.17 In developing countries, research ethics committees may have access to only limited administrative or financial support. Recent estimates suggest that the operating costs of one research ethics committee in the UK are £36,000 per annum, if both direct and indirect costs (such as time taken by committee members for review) are taken into account.⁵ This does not include start-up costs, reimbursement of costs of travel, costs of interacting with other committees, or of monitoring and evaluating approved projects. In the US, ethics review committees may cost up to US\$500,000 per annum to support.⁶ While the costs of running research ethics committees in developing countries will be much lower, such costs still represent a significant burden on limited resources.
- 8.18 To meet the financial costs, some research ethics committees receive regular funding from government. Others levy fees for reviewing research protocols. For example, in the UK, the Oxford regional research ethics committee charges pharmaceutical companies to conduct a review.⁷ Research ethics committees may charge a set fee for review or a variable fee, based on a proportion of the proposed research budget. While external sponsors generally recognise that set fees for reviewing research are a legitimate overhead cost, and some are encouraging such costs to be clearly identified in funding applications, they are often less willing to pay a proportion of the research budget for such review, particularly when this amounts to a significant sum.
- 8.19 Research ethics committees that levy fees may find it difficult to maintain their independence if fees are paid to the committee directly, rather than into a central fund, which can then be used for such matters as developing infrastructure, training and development for such committees. This possible weakening of independence may be the case even though the funds are intended for logistical support of the effective functioning of the committee. To meet this concern, in countries in which there is no central pool into which such levies may be paid, they could be paid to a local or national government and earmarked for support of research ethics committees.
- 8.20 Regardless of whether the financial support for research ethics committees comes from government, research institutions or as a result of levying fees for review, it is crucial that the independence of research ethics committees be maintained. **We conclude that there is a**

5 Squire SB (2001) Personal communication, Liverpool School of Tropical Medicine.

6 Wikler D (2000) Personal communication, World Health Organization.

7 Personal communication, Working Party fact-finding meeting in Oxford.

need for creative approaches to providing support, especially financial support, for research ethics committees, without compromising their independence. Sponsors should determine how they can meet the costs of ethical review without compromising the independence of the research ethics committee and should be responsible for meeting the costs of reviewing externally-sponsored research.

- 8.21 The activities of research ethics committees need not be confined to approving or rejecting proposals for research. They may also play an educational or advisory role by suggesting modifications to proposals that are consistent with ethical requirements. In addition, research ethics committees should ideally play some supervisory or monitoring role once projects have begun. If unable to do so, an alternative is to appoint an independent monitor (for example a clinician), to monitor compliance with the agreed protocol and to ensure that the participants in the research project are suitably protected, but funding would need to be made available for this. In our view, it is highly desirable that research ethics committees throughout the world should request annual reports of progress from researchers. However, we recognise that many research ethics committees in both developed and developing countries do not currently have the resources to undertake such reviews. Therefore, we urge sponsors to allocate appropriate additional resources so as to facilitate the conduct of an annual review of research.

Reviewing research in the sponsoring country and the country in which the research is conducted

- 8.22 In order to ensure that acceptable ethical standards are observed in externally-sponsored research, research should be approved through a system of ethical review of research in both the host and the sponsoring country. As regards the latter, if a sponsor provides funding, it must have the means of ensuring that the funds are being used in a manner that is ethically acceptable. However, the country in which the research is to be conducted must also be satisfied about the ethical acceptability of the research. **We recommend that externally-sponsored research projects should be subject to independent ethical review in the sponsor's country(ies) in addition to the country(ies) in which the research is to be conducted.**
- 8.23 The imbalance in power resulting from inequalities in resources discussed in Chapter 4 may extend to relationships between research sponsors, researchers and research ethics committees in developed countries on the one hand, and research ethics committees in developing countries on the other. For example, commercial pressures may be applied to committees in developing countries to use the same structures and procedures for ethical review as in the sponsoring countries. Guidance on research ethics committees in fact sets out a number of possible structures for such committees (Appendix 1 Table 4). Developing countries should, therefore, be able to adopt the structure(s) for research ethics committees that they consider will allow them to provide effective ethical review.
- 8.24 Difficulties may also arise when research ethics committees in developing countries are asked to review research before it is reviewed in the country of the sponsor. This may cause committees in developing countries to employ scarce resources to review research that the sponsor subsequently decides not to fund. On the other hand, once research has been reviewed in the sponsor's country, some research ethics committees in developing countries may be placed under pressure to concur with the opinion of the committee in the sponsor's country, particularly when reviewing forms of research of which they have limited experience.
- 8.25 Should there be disagreement between committees in the developed and developing country(ies), negotiation between the committees may be required. There should be mechanisms available to

facilitate such negotiation. At present such mechanisms, which are likely to benefit both host and sponsoring research ethics committees, are rare. Where there are irreconcilable differences between research ethics committees, a committee may choose not to approve the research. If a committee from a sponsoring country does not approve the research, the sponsor cannot fund it. If a research ethics committee from a developing country does not approve the research, then the research cannot be conducted within that country.

Developing capacity for reviewing the ethics of research

- 8.26 For research ethics committees to function effectively, committee members must receive adequate training. As many research ethics committees in developing countries have a rapid turnover of staff, regular training programmes for current and prospective members of committees are needed. A number of programmes are being established to develop expertise in the field of medical ethics and/or conducting ethical review. For example, the Fogarty International Centre of the National Institutes of Health (NIH) in the US is currently sponsoring training programmes in bioethics for faculties from developing countries. Towards the end of 2002, The Wellcome Trust will launch a funding initiative to support research into ethical and social aspects of conducting biomedical research in developing countries.⁸
- 8.27 The United Nations Development Programme (UNDP)/World Bank WHO Special Programme for Research and Training in Tropical Diseases (TDR) is addressing the need to strengthen the procedures for ethical review of research in developing countries through the training of key individuals in major research institutions.⁹ WHO's guidelines, which are available in Cambodian, English, French, German, Lao, Russian, Spanish, Thai, Turkish and Vietnamese, bring together previous recommendations concerning the minimum requirements for the proper functioning of ethics committees.¹⁰ The guidelines are currently being used in a number of regional fora which have been established to support the development of expertise in reviewing the ethics of research (see Box 8.2). In addition, regional workshops to train researchers and members of ethics review committees are currently conducted by the UNDP/United Nations Population Fund (UNFPA)/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction.
- 8.28 The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) is establishing networks within regions which will identify needs for training and education.¹¹ Each region has a forum, whose officers work with local governments, research institutions and participants in research and can represent the interests of research ethics committees at an international level (see Box 8.2).
- 8.29 Concerns have been expressed that training programmes for members of research ethics committees in developing countries, sponsored by a single developed country, may tend to reflect the views and procedures of the sponsoring country. **We recommend that international**

8 The majority of the research will take place in developing country locations where clinical or community oriented biomedical research is being done. An aim is to build capacity within developing countries to address ethical and social questions, and to increase the number of people with experience and training in this area.

9 Issues such as consent, standards of care and the protection of participants in research are part of a programme of training which also involves guidance on how to establish an effective research ethics committee.

10 World Health Organization (WHO) (2000) **Operational Guidelines for Ethics Committees that Review Biomedical Research**. WHO, Geneva. These guidelines define the role and composition of an ethics committee, detailing the requirements for submitting an application for review. Emphasis is placed on maintaining global ethical standards, while taking into account local variations in practice.

11 SIDCER was developed with contributions from WHO, European Forum for Good Clinical Practice (EFGCP), industry and CIOMS in conjunction with other institutions and associations. SIDCER works in co-operation with the established regional fora for ethical review and the WHO Regional Offices.

programmes and organisations, including WHO, continue to expand their current programmes for establishing, training and monitoring the development of research ethics committees. Funding should be provided to these international programmes for such purposes by bodies that sponsor research in developing countries.

BOX 8.2 Regional fora for developing the capacity for ethical review

A regional forum for ethics review committees in Asia and the Western Pacific (FERCAP) was established in January 2000. FERCAP has the objective of fostering an improved understanding and implementation of the ethical review of research by improving communication among ethics committees, acting as a collaborating centre and assisting in the implementation of relevant guidance. To date, it has sponsored a one-week training course in Bangkok in collaboration with a Thai and a Norwegian University.¹ Websites are being developed by FERCAP to assist in the dissemination of information. In addition to the regional fora, national bodies are being developed, for example FERCIT (the Forum for Ethical Review Committees in Thailand).

In Africa, a regional forum is being developed. PABIN (the Pan African Bioethics Initiative) aims to encourage the establishment of research ethics committees in countries in which they do not yet exist. It plans to conduct educational courses for members and potential members of research ethics committees in Africa.² The African Malaria Vaccine Testing Network (AMVTN) was set up in 1995 to assist in the planning and conduct of trials for a vaccine for malaria. It organises training courses in ethics for interested parties and will continue in this role, particularly while PABIN is developing.

In Russia and Eastern Europe, the Forum for Members of Ethics Committees in the Confederation of Independent States (FECCIS) was established in 2001. FECCIS plans to support the establishment of national and regional systems of ethical review, translate and distribute WHO's guidelines³ and develop training courses for medical students and research ethics committee members.⁴

Similar bodies have been set up in Latin America (The Latin American Forum of Ethics Committees in Health Research (FLACEIS)) and the Caribbean.

1 See FERCAP's objectives and activities at <http://www.fercap.org/> and 'The ethics of biomedical research' in **TDR News**, No. 63 (October 2000) at <http://www.who.int/tdr/publications/tdrnews/news63/ethics.htm>.

2 Chintu C (2001) Personal communication, PABIN.

3 World Health Organization (WHO) (2000) **Operational Guidelines for Ethics Committees that Review Biomedical Research**. WHO, Geneva.

4 The three-year plan for the Forum for Ethics Committees in the Confederation of Independent States (FECCIS) (2001–2003).

110 หน้าว่าง



Chapter 9

*What happens once
research is over?*

112 หน้าว่าง



Introduction

- 9.1 Much of the debate about the ethical issues which arise in externally-sponsored research in developing countries has focused on the protection of the participants during the study. However, there are also important issues concerning the welfare of those who have participated in the research and of the wider community once the research is over. The subsequent provision of interventions shown by the research to be successful, and continuing the provision of healthcare to research participants and to the wider community, are complex issues which confront researchers, research sponsors and providers of health services. Uncertainty about whether an experimental intervention will in fact prove to be successful, or be affordable, and the difficulty of guaranteeing that it will be available in the long-term have discouraged research sponsors from making commitments to participants and the wider community prior to embarking on any research. What makes these issues particularly difficult to resolve is that the possibility of introducing an intervention that has been shown to reduce morbidity or mortality may depend on support from external sponsors, other than those sponsoring the research, as well as action by national governments.
- 9.2 Most prominent among these various issues is the extent, if at all, to which diagnostics, medicines, surgical procedures and vaccines shown to be efficacious in research will be made available in the developing country in which the research was conducted. Many have voiced the opinion that participants in research should be guaranteed access to interventions shown to be successful once the study is complete, and that to fail to do so is a form of exploitation which is ethically unacceptable (see paragraph 9.21). However, in some circumstances, the subsequent provision either of interventions shown to be successful or of a better standard of healthcare¹ to participants in research and especially to the wider community is not straightforward. The provision of new medicines or better healthcare is primarily the responsibility of national governments. Sponsors of research are not therefore in a position to make unilateral decisions at the start of a trial without appropriate consultation. Nor are researchers usually in a position to guarantee provision of a new intervention once they have demonstrated its efficacy and safety. However, they may and frequently do act as advocates for the provision of a medicine or vaccine shown to be successful.
- 9.3 The main purpose of conducting clinical trials is to evaluate interventions that may be applied in the wider community, of which the participants in the trial are but a sample. While this may be true in general terms, there are often significant obstacles to the application of this principle in developing countries. A new or improved treatment may be expensive. If it is, the health authorities in an economically disadvantaged country are unlikely to be able to afford its distribution to the wider population. Researchers and sponsors must understand this and justify their decision to conduct research notwithstanding, if they wish to avoid the charge of exploitation.
- 9.4 Where a form of treatment which has been developed through research proves too expensive to be provided through the local healthcare system, what, then, are the responsibilities of the researchers and their sponsors? In particular, do they have any responsibility for ensuring that it is made more widely available after its efficacy has been demonstrated in a research study? Equally, if the provision of healthcare generally for participants has been improved during the study for the purpose of carrying out the research, is there a duty to maintain this level of healthcare after the research is over and, if so, on whom should such a responsibility fall?
- 9.5 What happens once research is completed will closely reflect how the research was conducted and in what context. The health and social conditions of those participating in the research, and the standards of care provided to participants during the study are relevant to what should be

1 i.e. better than the local standard.

provided for either these participants or the wider population at the completion of the study. When it is proposed to conduct clinical research in developing countries, the normal processes of review focus on the scientific merits and the ethical acceptability of the study. In addition, however, there is a growing consensus that the review of research should also address the issues that arise once the research is concluded.

9.6 While national and international guidance address some of these issues, the general nature of much of the guidance limits its usefulness to researchers or sponsors (Table 9.1 and Appendix 1 Table 5).

Table 9.1

International guidance on provision of healthcare after the research is over and the development of national expertise

Source	Text
CIOMS 'International Guidelines for Ethical Review of Epidemiological Studies' (1991)	<p>'Where findings could be applied in public health measures to improve community health, they should be communicated to the health authorities ... Research protocols should include provision for communicating such information to communities and individuals.' Principle 13</p> <p>'While studies are in progress, particularly in developing countries, the opportunity should be taken to train local health workers in skills and techniques that can be used to improve health services. For instance, by training them in the operation of measuring devices and calculating machines, when a study team departs it leaves something of value, such as the ability to monitor disease or mortality rates.' Principle 17</p>
CIOMS 'International Ethical Guidelines for Biomedical Research Involving Human Subjects' (1993)	<p>'As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made reasonably available to inhabitants of the underdeveloped community in which the research was carried out; exceptions to this general requirement should be justified ...' Commentary on Guideline 8</p> <p>'An ... objective of externally sponsored collaborative research is to help develop the host country's capacity to carry out similar research projects independently, including their ethical review ... external sponsors are expected to employ and, if necessary, train local individuals to function as investigators, research assistants, or data managers or in other similar capacities. When indicated, sponsors should also provide facilities and personnel to make necessary health-care services available to the population from which research subjects are recruited. Although sponsors are not obliged to provide health-care facilities or personnel beyond that which is necessary for the conduct of the research, to do so is morally praiseworthy'. Commentary on Guideline 15</p> <p>'Consideration should be given to whether the sponsoring agency should agree to maintain in the host country, after the research has been completed, health services and facilities established for purposes of the study.' Commentary on Guideline 15</p> <p>'The research protocol should specify what, if any, resources, facilities, assistance and other goods or services will be made available ... after the research, to the community from which the subjects are drawn and to the host country'. Commentary on Guideline 15</p>
WHO 'Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products' (1995)	<p>'The investigator is responsible for ... ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made'. Paragraph 4.1</p>
World Medical Association 'Declaration of Helsinki' (2000)	<p>'At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.' Paragraph 30</p>
UNAIDS 'Ethical Considerations in HIV Preventive Vaccine Research' (2000)	<p>'Any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. Plans should be developed at the initial stages of HIV vaccine development to ensure such availability.' Guidance Point 2</p> <p>'Strategies should be implemented to build capacity in host countries and communities so that they can practise meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process'. Guidance Point 3</p>

For example, while the revised Helsinki Declaration (2000) refers to the need to provide those who participated in the research with access to the interventions developed during the research, and the CIOMS 1993 Guidance (Guideline 8) refers to the need to make any product developed reasonably available to the underdeveloped community in which the research is conducted, the complexity of the issues warrants further consideration.² National guidance from countries such as South Africa and Uganda also tends to be framed in general terms.³ The US National Bioethics Advisory Committee (NBAC), however, in its report on clinical trials in developing countries, acknowledged implicitly the difficulties of making general recommendations to meet the needs of highly diverse situations.⁴ In this chapter we therefore consider the issues raised and discuss how they might be resolved. They are in turn:

- the continued provision of a higher level of healthcare
- the benefits to individual participants and to the wider community arising as a consequence of the research
- the availability of an intervention shown to be successful once the research is concluded
- the long-term safety of an intervention
- the responsibilities of sponsors of research to contribute to the development of national expertise in research.

The continuation of improvements in healthcare

- 9.7 Participants in research related to healthcare usually benefit from their participation in the research, even if they are in the control group. This may be especially the case in studies conducted in developing countries with poorly funded healthcare services, for it is often necessary to improve the local health-care system for the purposes of conducting research. For example, improved diagnostic facilities may have to be introduced to permit reliable diagnosis of the disease(s) being studied. The need for repeated clinical observations may require regular visits to a physician. Not only may this expose the participant to improved healthcare; a further consequence may be that other conditions from which a participant suffers may be diagnosed and treated even though these are unrelated to the specific research.
- 9.8 The provision of a better standard of healthcare may be particularly significant when the research is conducted with the prime objective of advancing scientific and medical knowledge without there being any immediate benefit or risk to the individuals or the community involved in the study. For example, research into the development of a vaccine may require knowledge to be gained of how individuals' immune systems respond to a naturally occurring infection. Such immunological studies are unlikely to be of immediate benefit to the participants in the research, and therefore particular value may be placed by the local participants on any improvements in healthcare that are provided as part of the study. Indeed, the provision of better healthcare may form part of the inducement to participate in research (see paragraphs 6.29–6.30).

2 World Medical Association (WMA) (2000) **Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects**, adopted by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. CIOMS (2001) **Draft Revision of the 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects**, CIOMS, Geneva.

3 See National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference) (1997) **Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda**, National Consensus Conference, Kampala, Uganda and South African Department of Health (2000) **Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa**.

4 National Bioethics Advisory Commission (NBAC) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission**, NBAC, Bethesda, Maryland.

- 9.9 Where research studies are on a large scale, the benefits of improved healthcare provided during the research may extend to the whole community, including those not directly involved in the research. Careful attention needs to be given to how such benefits are integrated into existing healthcare. For example, it may be necessary to improve the referral systems and diagnostic facilities at outlying centres. Alternatively, routine programmes of immunisation may need to be strengthened before trials of vaccines can be conducted.
- 9.10 During the study, the researchers can contribute directly to the strengthening of local healthcare facilities. In making such a contribution, however, careful consideration needs to be given to how sustainable any changes and improvements introduced for the purposes of the research might be. This is because any improvements are usually financed out of the research funds and, thus, may not be sustained once the research is completed. Much ill-feeling may be generated, and further research in the particular community compromised, if, at the end of the study, the researchers leave and the improvements to healthcare are not sustained much beyond the end of the study.
- 9.11 To what extent healthcare improvements should be sustained after the research is completed, and by whom, are difficult issues for researchers and sponsors. The CIOMS Guidelines (1993) (Guideline 15) states that consideration be given to the maintenance of health services and facilities in the host country once the research is over (Table 9.1). Sponsors are rarely in a position to make open-ended commitments beyond the duration of the study, particularly with regard to the maintenance of facilities or the provision of medicines. However, as a minimum, at the outset of the research, thought should be given to the impact which any temporary improvement in the quality of healthcare might have and whether this can be maintained once the study is over.
- 9.12 One real contribution which researchers and sponsors may be able to make is to increase the number of people able to contribute to healthcare and to assist the development and enhancement of their skills and expertise so that there is some potential for a sustained improvement in healthcare services after the study is completed. **We endorse the CIOMS Guidelines (1993) (Guideline 15) and recommend that sponsors of research should require that the development of local expertise in healthcare is an integral component of research proposals. Consideration should be given to the extent to which any strengthening of local healthcare facilities can be done in such a way that the changes are sustainable in the local context once the research is over.**

Adverse effects

- 9.13 On occasions, a participant in a study may suffer an adverse effect as a consequence of an intervention under evaluation. Clearly, during the study the researchers have a responsibility to care for those who may suffer such adverse effects arising from the research. But, in our view this responsibility extends also to those who suffer such adverse effects after the trial is formally ended, and to those who suffer the chronic consequences of adverse effects experienced during the study. If the adverse effect is serious, it may be detected during the course of the study, in which case the research may be halted earlier than originally intended, either by the researchers themselves or after advice from the Data and Safety Monitoring Committee (DSMC). In the case of studies of a particular treatment, it may be relatively straightforward to resume treating such participants with the previous form of treatment.

Compensation

- 9.14 The question of compensation for those injured or placed at increased risk of harm in the future as a result of research needs to be addressed. This issue was raised recently during the course of



a trial of a vaccine for malaria involving Gambian infants. Analysis of data from surveillance of participants from a pilot trial obtained after the main trial had started, suggested that vaccinated children were *more* at risk of malaria than children in the control group.⁵ In this case, the UK Medical Research Council (MRC) provided further funds so that surveillance of participants in the trial could be intensified and facilities for the treatment of malaria in the area of the study improved. In addition, surveillance was continued for two years after the trial had been completed. Fortunately, although recipients of the vaccine were not protected from malaria by the vaccine, they were not found, on prolonged surveillance, to be at any enhanced risk of infection. No question of compensation thereby arose. Less favourable outcomes, which might raise the need for compensation, might only be revealed by routine monitoring of the participants once the trial is over.

- 9.15 It is also possible that a vaccine, a treatment or another form of intervention may be beneficial in the short term, but later have harmful side-effects. In addition, short-term side-effects may recur later. An example is the possibility that exposure to antiretroviral therapy in fetal or early life to prevent the transmission of HIV from mother to child may be associated with adverse effects in later life. This particular possibility is currently being addressed in developed countries through national and international collaborative studies, since the risk of adverse events may be small and would not necessarily be detected in a single study. If the therapy is widely used, even a small risk can pose a significant problem.
- 9.16 Researchers and their sponsors have an ethical obligation to do everything possible to minimise any harm to participants in research. If a participant in research is harmed during the course of the research, what ethical duties arise? In particular, who has responsibility for meeting any financial needs which the participant may have, for example, to pay for medical care or lost employment?⁶ In general, responsibility for the healthcare of the participants is shared between the researchers and the local health authorities. But, if unexpected consequences do arise during the research, it is not always clear how the financial burden should be apportioned. Much of the national and international guidance addresses issues of compensation explicitly. For example, the Indian guidance stipulates that research proposals must include a mechanism for financial compensation to cover all foreseeable and unforeseeable risks (see Appendix 1 Table 3). In our view, issues about levels of compensation and who has the responsibility to provide it must be carefully considered and resolved between all those involved in the research before it begins.

Long-term surveillance

- 9.17 It is unusual for a research project in a developing country to include any long-term surveillance of those participating in research after a research study has been completed. Clearly interventions may have long-term as well as short-term consequences. In some circumstances the long-term consequences may be deleterious, even though the short-term consequences are beneficial. In trials in Guinea Bissau and Senegal, high-titre (high potency) measles vaccines, when given at a younger age than normal, induced a better antibody response at that age than conventional measles vaccines. On the basis of these trials, more widespread early use of high-titre vaccines was recommended in situations in which there were high rates of infection with measles occurring earlier in childhood than the normal age at which children would be vaccinated. However,

5 Leach A, Drakeley CJ, D'Alessandro U, Fegan GW, Bennett S, Ballou WR *et al* (1995) A pilot safety and immunogenicity study of the malaria vaccine SPf66 in Gambian infants. *Parasite Immunology*, 17: 441–4; Bojang KA, Obaro SK, Leach A, D'Alessandro U, Bennett S, Metzger W *et al* (1997) Follow-up of Gambian children recruited to a pilot safety and immunogenicity study of the malaria vaccine SPf66. *Parasite Immunology*, 19: 579–81.

6 UK public sector research funding bodies such as the MRC may not, as a matter of principle established by government, offer advance indemnities nor take out commercial insurance for non-negligent harm. The MRC only offers the assurance that it will give sympathetic consideration to claims in respect of non-negligent harm arising from an MRC-funded trial.

long-term surveillance of those participating in the studies showed that girls who received the high-titre vaccines had an increased rate of mortality several years after the vaccination, from causes not obviously related to measles. This unexpected adverse effect caused the high-titre dose vaccines to be withdrawn from general use.⁷

- 9.18 Risk of severe infection following early preventive measures is a particular concern in the case of malaria. Ordinarily, natural and lasting immunity to malaria follows repeated exposure to the disease for those who survive such exposures. Early preventive measures, by inhibiting repeated exposure, may enhance rates of morbidity and mortality and the likelihood of severe infection in later childhood. Several large field trials have shown that bed-nets and curtains treated with insecticide reduce overall mortality in young African children by 20–30%. There is a theoretical possibility, however, that, as a consequence of this early protection, such children may be at increased risk of contracting severe malaria in later childhood. It is still unclear whether this is in fact the case.
- 9.19 The two examples cited raise the question whether investigators have an ethical obligation to undertake long-term surveillance of the populations in the study. The planned surveillance of a trial population should be so designed as to enable researchers to observe both early and late effects of the intervention being tested. Ideally, all those in a trial would be followed for an indefinite period in order to detect any long-term effects of the intervention being studied. This is rarely possible even in developed countries.⁸ In practically all developing countries and many developed countries, such long-term surveillance has to be specifically designed and operated and is not possible within the routine system of healthcare.
- 9.20 However, a paradoxical situation may arise. If an intervention is shown to be efficacious in the short term, it may be considered unethical to continue to maintain a control group, after such efficacy has been demonstrated (see paragraph 9.27). However, when the intervention is offered to those in the control group once a trial is completed, the opportunities for longer-term observation and for the detection of later deleterious effects are lost because there is no longer a control group for comparison with the participants who received the intervention. We conclude, therefore, that the course of action adopted in any particular study will depend upon the particular circumstances: the likelihood of long-term adverse effects will have to be weighed against the likely short-term benefits. This judgement, which is not confined to clinical trials in developing countries, will have to be made on a case by case basis. It will often be difficult to make and the correct balance is often only apparent with hindsight.

Provision of an intervention once the study is over

- 9.21 A question that researchers, sponsors and research ethics committees have to consider in research related to healthcare concerns the availability of an intervention shown to be successful to the participants in the research once the research is over. Because resources for healthcare are scarce in developing countries, this issue is often particularly difficult to address. We have seen that, for many poor people, participation in a trial may offer access to significantly better medical care and treatment (paragraphs 6.29–30). The cessation of such care and treatment, once a trial is over, has been widely criticised as exploitation of vulnerable people who generally have very limited access to healthcare and who will seldom be in a position to negotiate the extended provision of better medical care and treatment at the termination of a clinical trial.⁹

7 Knudsen KM, Aaby P, Whittle H, Rowe M, Samb B, Simondon F *et al* (1996) Child mortality following standard, medium or high titre measles immunization in West Africa, *International Journal of Epidemiology*, 25: 665–73.

8 The linkage of mortality and morbidity data with research studies over the long term poses substantial problems and is rarely feasible, except in specific cases, such as the link between mortality and cancer registries in the UK.

9 See, for example Glantz LH, Annas GJ, Grodin MA and Mariner WK (1998) Research in developing countries: taking 'benefit' seriously, *Hastings Center Report*, November–December: 38–42.

- 9.22 An even more difficult issue, however, is the extent of the obligation to make an intervention found to be efficacious in trials available to the wider community. Is there an ethical responsibility to ensure that an effective treatment or procedure is provided to the wider community after research is over and on whom does such a responsibility fall? In some circumstances, researchers may be in a position to take on a continuing obligation to the community in which the study was undertaken such as providing preferential access to a treatment that was developed with the co-operation of the community. It is usually difficult, however, to secure open-ended commitments to supply, for example, a new vaccine, beyond that to be used in the trial.
- 9.23 In the following sections, we consider what ought to be provided, and whose responsibility any such provision should be, to three groups of people: members of the control group in a trial, all of the participants in the research, and the wider community in which the trial took place. We first address the issue of the control group because this raises discrete questions that apply to research related to healthcare wherever it is conducted. We then go on to consider the provision of interventions to all of the participants in research and then to the wider community.

Providing interventions to the members of control groups

- 9.24 If the new intervention is shown in the trial to offer a benefit, is there an ethical obligation to offer it to the control group once the trial is complete, if they are still in a position to benefit from it? We consider that there is indeed such an obligation. In fact, such an undertaking is often given by researchers at the start of a study and may serve to persuade people to take part in the research. The nature and degree of the commitment would depend on the details of the particular study. For example, where a new medicine is being tested, treatment of the control group may be indicated when the new medicine has been demonstrated to be better than the previous one. If the new treatment is judged to be inferior, then, on the same principle, it may be appropriate to offer to treat those who received the new treatment with the standard treatment. In all cases, it should be made clear, as part of the process of obtaining consent, what is to be offered to those in the control group at the completion of the trial, and the circumstances in which it will be offered, before participants are asked to agree to take part.
- 9.25 The principle that those in the control group should be given the opportunity to benefit from an intervention found to be efficacious in a trial, is widely accepted in international guidance on controlled trials (see paragraph 5.13). Ordinarily, this is relatively straightforward for the researchers to arrange. For example, in trials of bed-nets impregnated with insecticide against malaria, those in control groups were given such nets once it had been demonstrated that the provision of nets reduced child mortality.
- 9.26 However, exceptions might arise for example if, by the end of the trial, some or all of those in the control group are not at an age, or stage of disease, to benefit from a particular treatment. In addition, it may sometimes be logistically difficult to make the intervention available to all the members of a control group. This was the case, for example, in a trial of a vaccine against infection with *Haemophilus influenzae* in The Gambia.^{10,11} It was argued that not only would it have been difficult to locate and vaccinate those in the control group, who were entered into the trial shortly after birth, but also that, by the end of the trial, they had passed through the ages of greatest risk of infection and thus vaccination would confer very limited benefit.
- 9.27 Vaccine trials also present a further difficulty. Because most vaccines induce an immunity that declines with time, there are strong scientific grounds, when a vaccine has shown to be effective,

10 McAdam K (2002) Personal communication, MRC Laboratories, Fajara, The Gambia.

11 *Haemophilus influenzae* causes a range of diseases including pneumonia and bacterial meningitis.

for maintaining the control group so that the duration of protection induced by the vaccine can be determined. However, when the control group remains at significant risk if not vaccinated with a vaccine shown to be efficacious in the short term, such an approach would be unethical. We propose, therefore, that those in control groups should be offered vaccination with the effective new vaccine on completion of the trial, if they are still at significant risk of the disease against which the vaccine is directed. As we have said, we consider that there is an ethical obligation to provide a control group with an intervention when it would benefit them (paragraph 9.24). **We conclude moreover that it would not be ethically acceptable for any study to begin without a decision having been made about whether or not those in control groups will be offered an intervention shown to be successful on completion of the trial where relevant and appropriate. Participants should be informed of the decision as part of the process of obtaining their consent.**

Providing interventions to all the participants in a research project once the study is over

- 9.28 Participants in research may have conditions that require ongoing treatment. In such cases, after a trial has ended, is there an obligation to continue to provide an intervention that has been shown to be effective to all the participants? Whose responsibility ought such provision to be? The revised Helsinki Declaration (2000) states that at the end of a study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified in the study. Extensive criticism has been levelled at this statement. While it is commendably aspirational in concept, guaranteeing the provision of an intervention which has been demonstrated to be successful may not be possible, especially in relation to ongoing treatment for chronic disease.
- 9.29 The NBAC Report¹² makes more specific recommendations about the provision for participants of treatment which has proved to be successful (Appendix 1 Table 5). It states that researchers, before the initiation of the trial, should endeavour to secure access for all participants to effective treatment after the trial and that the lack of any such arrangements should have to be justified to a research ethics committee.¹³ The Report also recommends that research proposals should include an explanation of how any new treatment which proves to be successful will become available to some or all of the host country's population. It goes on to require that researchers must justify to the relevant research ethics committee why the research should be carried out, if this is not thought possible.¹⁴ The National Guidelines for Health Research in Uganda go further. They state that the researcher must make every effort to ensure that a beneficial intervention is made available to the participants, as well as making all reasonable effort to secure its availability to the local community.¹⁵
- 9.30 The decision whether to make treatment available to participants in a clinical trial after the trial has been concluded will depend first and foremost on the outcome of the research. In practice, it may also be influenced by the cost of providing the intervention and supervising its administration. If prolonged treatment is involved, possibly for the rest of a participant's life (such as antiretroviral therapy for patients infected with HIV, or anti-hypertensive medicines for those with hypertension, which affects 50–10% of West African adults), it may be beyond the resources of the local health services.

12 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I Report and Recommendations of the National Bioethics Advisory Commission**, Bethesda, Maryland, USA.

13 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.1.

14 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.2.

15 National Consensus Conference on Bioethics and Health Research in Uganda (National Consensus Conference) (1997) **Guidelines for the Conduct of Health Research involving Human Subjects in Uganda**.



9.31 On examination, it might be shown that, if a pharmaceutical company were to provide the medicines required for the research, and the treatment were shown to be successful, this would be commercially advantageous, such that the costs of continuing to provide the treatment to participants in the trial could be offset. We repeat that it is very important that these issues be considered at the planning stage of any research, rather than debated or negotiated during the study or at its end. **We therefore endorse the NBAC recommendation that researchers should endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee.**¹⁶

Providing interventions to the wider community and beyond

9.32 Can it be ethical to conduct research when there is little chance of making treatment shown to be successful available to the wider community? Researchers and sponsors of research have looked to international and national guidance to help them to resolve this issue. However, as we have noted, international guidance is principally in a general form and frequently difficult to apply in practice. There are, moreover, many social, political and economic factors which will influence the likely availability of a treatment shown to be successful and not all of these can be anticipated.

9.33 Several questions arise from consideration of the guidance on the availability of an intervention shown to be successful after the completion of the research, with respect to the range and scope of the responsibilities, and on whom such responsibilities fall:

- Should provision of an intervention shown to be successful be limited to the participants in research, or extended to others in the same community? If the latter, by whom?
- What is the degree of efficacy that an intervention must demonstrate, in order to warrant extensive distribution and who should provide it?
- Should all with a perceived need in the country receive the intervention and if so, for how long and who should provide it?
- Should the intervention be provided to other (neighbouring) countries which could benefit from it and who should provide it?

These questions will become increasingly pressing as more interventions, which have the potential to benefit large numbers of people are tested in developing countries. It is clearly difficult to formulate general guidance which satisfactorily addresses the wide range of different forms of intervention.

9.34 A fundamental problem that must be acknowledged is that current guidance fails to reflect the reality that only rarely does a single research study lead to the discovery of a new intervention that can be introduced promptly into routine care.¹⁷ For example, before mefloquine was registered as an antimalarial medicine, the WHO Special Programme for Research and Training in Tropical Disease (TDR) conducted 18 studies on three continents. Secondly, even when clinical trials have established the safety and efficacy of an intervention, there is likely to be a need for additional research studies to define the place of the new intervention in the healthcare system. Further, those participating in the trial may not be representative of the wider population, or the intervention may not be equally efficacious in another setting. For this reason, the trial may need to be repeated elsewhere and in a different setting. Research may also be necessary to determine

¹⁶ National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.1.

¹⁷ This point also has a bearing on the question of whether it will be appropriate to continue to provide a successful treatment to the research participants once the research is over (see paragraphs 7.24–7.27)

the most effective and feasible means of making the intervention available and of achieving high uptake and acceptance by the local population. In addition, while clinical trials may show that, for example, a new antimalarial medicine is highly efficacious, policy-makers may decide to hold it in reserve while current treatments are still proving effective in order to delay resistance to the new treatment developing.

- 9.35 The cost effectiveness of any new intervention will also affect any decision as to its availability on a wide scale. One example of the need for cost-benefit analysis is provided by the early trials to assess the efficacy of antiretroviral treatment in reducing the transmission of perinatal HIV. The trials were performed in settings where appropriate counselling and facilities for HIV testing in pregnant women could be ensured, and where the infrastructure was such that the women were seen in hospital prior to delivery and the babies were delivered in the hospital with appropriate support and care.¹⁸ However, this setting is not typical for women in many developing countries. A significant proportion live in rural communities with no access to counselling and testing facilities, and many undergo home deliveries. Nevertheless, following trials demonstrating the efficacy of the treatment, programmes to make the treatment available more widely were set up. These programmes were funded by a large number of national and international agencies, and assessed the feasibility and obstacles that needed to be overcome before the intervention could be extended into the wider community and nationally.
- 9.36 A further difficulty is that the responsibility for making a vaccine, treatment or other intervention available will not lie solely with any one group. If a national government has agreed to allow a trial to take place, it presumably accepts some responsibility to act on the results. However, some form of external aid or subsidy may be necessary before any intervention can be made more widely available and there will need to be negotiations between the various interested parties.

The role of researchers

- 9.37 There is general agreement that researchers have some responsibility regarding the provision of an effective intervention after a trial has ended, but disagreement about how far that responsibility extends. Certainly, the main function of the researchers is to undertake research. They cannot be expected to adopt a leading role in making effective interventions available. Nevertheless, most people would agree that the researcher should present findings in such a way that healthcare policy-makers can understand their implications and, at the least, the findings can be used for advocacy purposes with respect to the future provision of the intervention.
- 9.38 Fundamentally, it is policy-makers who have the prime responsibility to implement changes in healthcare and to seek evidence to inform their decisions. For example, as early as the 1950s, clinical research demonstrated that the administration of at least two doses of tetanus toxoid to pregnant women could prevent neonatal tetanus. Although most health authorities in developing countries have adopted this practice, WHO estimated that there were still 270,000 cases of neonatal tetanus in 1998.
- 9.39 While researchers are generally not in a position to translate their research findings into action when an intervention proves to be efficacious, they can draw attention to problems which have been neglected, or conditions whose impact has been underestimated, and demonstrate that there are feasible solutions. For example, a package of simple affordable measures which reduced child mortality was identified in Nigeria in the 1960s, some of which were quickly adopted by a number of developing countries. These measures later formed the basis of UNICEF's global strategy for its programme in child survival based on GOBI-FFF (growth monitoring, oral

18 Shaffer N, Chuachoowong R, Mock PA, Bhadrakom C, Siriwasin W, Young NL *et al* (1999) Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *Lancet*. 353(9155) 773–80.

rehydration, breastfeeding, immunization, food supplementation, family planning, and female education). The researchers could not ensure that the Nigerian health authorities would adopt the methods demonstrated by their studies. In fact, Nigeria has been very slow in implementing the programme as originally designed or as modified by UNICEF.¹⁹ Despite this, the research was very valuable in its advocacy of improved care for children. The iodination of salt to combat goitre in Nigeria (see Box 9.1) provides a further example of, on the one hand, the important role as advocates of better healthcare which researchers can play, while on the other hand, illustrating the limited influence that researchers may have in bringing about the prompt provision of effective interventions.

BOX 9.1 Iodination of salt

In 1975 a group of scientists led by the Chairman of the Nigeria Medical Research Council presented research data to the Nigerian Department of Health which revealed the high prevalence of goitre in the country. Attention was drawn to the impact of iodine deficiency not only in causing goitre but also in reducing the intellectual capacity of children born to iodine-deficient mothers. The group urged the government to introduce iodination into the two salt factories in which the government had investments. UNICEF had offered to cover the cost of modifying the equipment to accommodate the iodination process. It took a further 15 years of lobbying before the Ministry of Health took action.¹

1 Lucas A (2001) Personal communication, Harvard University.

- 9.40 A further important role of researchers is to inform local health authorities and participants about the results of their research at the end of a study. This should be accompanied by an explanation of the implications of the results for future healthcare, or prevention of disease in the community. How such information is provided will vary in different circumstances, but as well as a written report and a verbal presentation, researchers have an obligation to answer any questions that participants or other members of the community may have about the nature and significance of their findings. The appropriate forum for this is often a public meeting. It should be noted that failure on the part of researchers to present the results of a trial is a frequent reason for participants' unwillingness to participate in any subsequent research.

The role of sponsors, international agencies, governments and other bodies

- 9.41 If sponsors of research were required to fund the future provision of interventions shown to be effective to research participants or the wider community, many would cease to support such research. Sponsors from the public sector, such as the UK MRC or US NIH, would simply be unable to bear the costs involved without curtailing other research. Although the financial resources of many pharmaceutical companies are large, many of them would be equally reluctant to take on the additional burden of long-term commitment.
- 9.42 Any intervention shown to be effective in a research study may not be generally adopted because of cost. Although a successful national trial of bed-nets treated with insecticide in The Gambia reduced overall child mortality from malaria by approximately 30%, it was decided by the researchers, sponsors and the Gambian Ministry of Health that when the research was implemented nationally the cost of the insecticide would have to be recovered because the Ministry could not afford to provide free insecticide indefinitely. Charging for insecticide led to a reduction in the number of young children sleeping under an insecticide-treated net from around 70% to 20%.²⁰

19 Lucas A (2001) Personal communication, Harvard University.

20 Cham K, Olaleye B, D'Alessandro U, Aikins M, Cham B, Main N *et al* (1997) The impact of charging for insecticide on the Gambian national impregnated bednet programme, *Health Policy and Planning*, 12: 240-7.

- 9.43 It should be borne in mind that while interventions may initially be too costly to be made available, costs may subsequently fall. This was the case with the hepatitis B vaccine used in The Gambia (see Box 1.3). On occasions, manufacturers of vaccines or sponsors of research might agree to supply substantial quantities of a vaccine free or at subsidised cost after the successful completion of a trial. This was done, for example, following trials of *Haemophilus influenzae* (Hib) vaccine in The Gambia, but it was not possible to secure an initial commitment beyond five years.²¹ The issue of how large a population might be included in such a scheme also arises. The Gambia is a small country (about one million inhabitants), and commitments extending to much or all of the country have been secured following trials there. Such a commitment may be much more difficult to secure in a larger country, for example Nigeria or India, such that it might have to be limited to a region, or part of a region. The pharmaceutical industry is involved in various donation programmes and partnerships (see paragraph 2.35). An example is the ongoing donation of Ivermectin. This treatment, originally developed for treating animals for worm infestation, was found to be highly effective against onchocerciasis (river blindness) in humans, but was too expensive for use in developing countries. However, the pharmaceutical company that produced the medicine decided to provide it at no cost for the treatment of onchocerciasis and WHO has managed the distribution to countries in onchocerciasis-endemic areas.
- 9.44 In some circumstances, the results of a successful study may influence national policy and bring pressure to bear on providers of health services to make the intervention available. In a recent study in Uganda, oral nevirapine was administered to pregnant women infected with HIV at the onset of labour, and the newborn babies received nevirapine syrup within 48–72 hours after delivery. The study showed a 50% reduction in transmission of HIV-infection from the mother to the baby at 14–16 weeks in the group receiving nevirapine, compared to the control group which received AZT alone. The Ugandan government acted on the findings of the study and introduced a policy of providing the treatment involving nevirapine to all pregnant women who were HIV positive. The cost of treatment is relatively low, about US \$4 per person, but this is still more than most countries in which HIV is endemic can afford. The pharmaceutical company concerned has recently announced that it will offer the medicine free of charge for use in the prevention of transmission of HIV from mother to child in developing countries.²² That said, the programmes of treatment do not depend merely on the cost of the medicines. It is the voluntary counselling and testing, an integral part of these programmes, as well as the need for an appropriate infrastructure for the delivery of healthcare that account for the greatest cost. Finally, quite apart from considerations of cost it is important also to bear in mind the broader benefits for women and infants that may arise from a more widespread improvement in antenatal care. These examples have led us to conclude that the fact that a particular intervention is currently expensive should not necessarily rule out the possibility of its being evaluated in a developing country.
- 9.45 As we have seen, the costs of some interventions shown to be successful may not decline significantly until some time after the conclusion of the research. To describe all such research as therefore unethical may lead to the loss of opportunities to improve healthcare. At the same time, several factors would need to be taken into account before the testing of costly medicines could be justified, including the extent of the prevalence of the condition being studied in those participating in the research, whether the disease is acute or chronic, and the complexity of and feasibility of delivering the regime of treatment. In particular a research ethics committee would need to be persuaded of the need to carry out the study in a particular community. Whether or not provision for ongoing

21 McAdam K (2002) Personal communication, MRC Laboratories, Fajara, The Gambia.

22 Boehringer Ingelheim has offered to supply VIRAMUNE® (Nevirapine) free of charge for the prevention of mother-to-child transmission in developing economies. Supplies of medicines have already been made to the Republic of Congo and to Senegal.

treatment beyond the end of the trial are in place should also be clearly explained to prospective participants before their consent is sought.

- 9.46 While the prime responsibility for continuing healthcare in a community lies with the local health authorities, we take the view that researchers also have some responsibility for what follows from the research which they conduct. A close dialogue should be maintained with the local authorities before a trial begins and at all stages of the trial. For an intervention which has a low cost, the issue of its continued availability to participants may not arise, except for concerns as to whether there is the necessary infrastructure to deliver the intervention, although in poor communities this is often a very significant consideration. For interventions which have a high cost, as we have seen, continued availability may be much more problematic.
- 9.47 Of particular concern has been the suggestion that some clinical trials in developing countries have been conducted not for the benefit of those in developing countries but largely for the benefit of those in developed countries. A possible example may be the evaluation of low cost schedules of HIV treatment (see Box 1.2). While finding less expensive, but effective, treatments for infection with HIV is a high priority for developing countries, it would also be of significant interest to developed countries. It should be recalled that the price of cheaper treatments may still be beyond the resources of most developing countries.
- 9.48 **In light of the issues discussed above, we recommend that the following issues are clearly considered by researchers, sponsors, national healthcare authorities, international agencies and research ethics committees as part of any research protocol before research relating to healthcare involving the testing of new interventions is undertaken:**
- **the need where appropriate to monitor possible long-term deleterious outcomes arising from the research, for an agreed period of time beyond the completion of the research**
 - **the possibility of providing participants with the intervention shown to be best (if they are still able to benefit from it), for an agreed period of time**
 - **the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful.²³**
- 9.49 **We endorse the NBAC recommendation that research proposals submitted to those committees should include an explanation of how new proven interventions could be made available to some or all of the host country population and that investigators should justify to the relevant research ethics committee why the research should be carried out if this is not thought possible.²⁴**

The development of expertise in research

- 9.50 In 1990, the Commission on Health Research for Development identified the strengthening of expertise in research as 'one of the most powerful, cost effective and sustainable means of advancing health and development'.²⁵ During the decade which followed, efforts were made to strengthen expertise in research by national and international organisations. However, these

23 This consideration is especially important for expensive interventions.

24 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.2.

25 Cited in Health Research for Development: the continuing challenge, a discussion paper prepared for the **International Conference on Health Research for Development**, 10–13 October 2000, Bangkok.

efforts have been criticised for being fragmentary and not sufficiently endorsed and advanced by individual countries.²⁶ Indeed, very few developing countries have a systematic plan for developing such expertise. Despite the great need for research to identify the most effective healthcare interventions for developing countries, the extent of expertise to undertake this task at a local level is severely limited. This is due largely to insufficiently trained personnel and a lack of a critical mass of researchers. The few who are well trained and able are often in great demand and may be recruited by multinational companies or international health agencies, further reducing the expertise available for areas of national priority.²⁷ It is very important, therefore, that research in developing countries, particularly when sponsored by developed countries, is used as a platform for enhancing the skills of scientists in those developing countries. The concept of 'safari research', in which the researcher from a developed country visits a developing country merely to collect samples or data to be studied elsewhere, is ethically unacceptable.

9.51 Genuine partnerships should be promoted in order to strengthen expertise in research and institutional development and to maximise opportunities for the transfer of skills and knowledge. Genuinely collaborative research projects generate opportunities for training and for developing human resources. Such collaborations can increase self-reliance in developing countries, thereby enabling local specialists to identify areas needing research and to develop local solutions to public health problems. The development of operational guidelines for healthcare, systems for surveillance and management flow-charts are potential by-products which in turn contribute to the improvement of healthcare systems and the ability of countries to respond to their public health needs.

9.52 Once research is completed, there are occasions on which complicated and expensive research equipment may be left behind, or donated by the researchers from the developed country. If local scientists and technicians have not received sufficient training to maintain and use the equipment effectively, or if resources for maintenance of equipment are not available, the opportunity for improving the ability to conduct research locally will be lost. Funds for the maintenance of equipment and development of appropriate training programmes need to be included in the costs of the original research project. Equally, the costs of facilitating training, so as to ensure that equipment can be used and is maintained beyond the particular research project, should be considered. We note that guidance such as that of the Medical Research Council of South Africa (2002)²⁸ explicitly emphasises the need for the development of research expertise to be addressed before research is conducted. **We recommend that external sponsors of research should require that the development of expertise in research be an integral component of all research in developing countries. Consideration should also be given to the development and support of expertise so that equipment obtained for the purposes of a research project can continue to be used and maintained.**

26 Neufeld V and Johnson N (eds) (2000) **Forging Links for Health Research. Perspectives from the Council on Health Research for Development**, International Development Research Centre, Ottawa, Canada.
 27 Neufeld V and Johnson N (eds) (2000) **Forging Links for Health Research. Perspectives from the Council on Health Research for Development**, International Development Research Centre, Ottawa, Canada.
 28 Medical Research Council of South Africa (2002) **Guidelines on Ethics for Medical Research: General Principles**, Medical Research Council of South Africa, Tygerberg: Paragraph 11.4.4i.



Conclusions and recommendations

128 หน้าว่าง



Chapter 10

Conclusions and recommendations

130 หน้าว่าง



Introduction

- 10.1 Many people in developing countries suffer from poor health and reduced life expectancy. Poverty, coupled with limited scientific, administrative and political development often makes it very difficult for developing countries to improve healthcare. Those who seek to improve the health status of developing countries do so against this background, in which poor health is a reflection of the larger inequality. We have focused on one aspect of healthcare, that of research. Developing countries urgently need research related to healthcare which addresses their burden of disease. It is therefore axiomatic that externally-sponsored research that seeks to bring health benefits, should, with appropriate safeguards, be encouraged in developing countries. We consider, moreover, that there is virtue in research which provides not only direct benefits to participants such as treatments for specific health needs but also indirect benefits arising from the influx of resources into a local community and the enhancement of expertise in research.
- 10.2 We ask how the conduct of healthcare research in developing countries, much of which is funded by sponsors in developed countries, can be consistent with principles of justice. Our primary focus is not on the existence of injustice on a global scale but on its implications for those who have the power to act, whether within or outside of developing countries, including governments, research councils, private companies and researchers. The inequalities in resources between external sponsors of research into healthcare, and communities and governmental authorities in the developing countries, will often be so great that there is a real risk of exploitation in the context of externally-sponsored research. It is crucial therefore that the four principles which form the ethical framework for this Report: the duty to alleviate suffering; the duty to show respect for persons; the duty to be sensitive to cultural differences and the duty not to exploit the vulnerable are respected when research is planned and that appropriate safeguards are put in place.
- 10.3 The Working Party has made a number of recommendations to guide external sponsors of research related to healthcare. While these recommendations are, for the most part, directed to external sponsors, this is not to suggest that the principles on which they are based are not equally applicable to internally funded, national research. The recommendations, taken together, should be regarded as a framework for the ethical conduct of research, whoever the sponsor might be.
- 10.4 Our central aim has been to consider how individuals and organisations from developed countries should conduct themselves when sponsoring or undertaking research related to healthcare in developing countries. We have examined the ethical issues raised by externally-sponsored research and considered ways in which they might be resolved. The disparity between the resources and power of the external sponsor of research and the developing country has been central to the discussion. We recognise that external sponsors, whether they be multinational pharmaceutical companies or publicly funded research organisations, may differ in their motives for undertaking research related to healthcare in developing countries. Despite these differences, we consider that all externally-sponsored research should be required to fall within the ambit of the national priorities for research related to healthcare within developing countries, unless the reason for not doing so can be justified to the appropriate research ethics committee within that country. Not only must the people who are part of that research be treated with respect, but the balance between the interests of these individuals and the interests of the wider community from which they are drawn must be carefully weighed.
- 10.5 When planning and conducting research, researchers and their sponsors have a duty to recognise the importance of national and local cultures and social systems, values and beliefs. In addition, external sponsors have an obligation to educate and train members of the local and national communities in the methods and skills of conducting research. The need for research projects to

be subjected to review as to their ethical propriety is paramount. There is an urgent need for further education and training to ensure that those in developing countries are able to discuss ethical issues effectively with external sponsors and others and to have mechanisms in place to deal with issues that arise. Most importantly, research ethics committees in developing countries have the responsibility of sanctioning only that research which is appropriate and of challenging and preventing research that is not.

- 10.6 The four main topics of our Report – standards of care, consent, the ethical review of research, and what happens when the research is over – emerged as we examined the subject in detail and in response to questions raised during our deliberations. Some of the recommendations which we make on these topics have been directed to particular agencies with a view to their taking them forward. We also set out an agenda for action by those in developing countries so as to develop expertise in the conduct of research and effective procedures for the ethical review of research proposals.

Healthcare economics

- 10.7 The major inequalities in health which exist across the world are closely related to levels of social and economic development. The burden of disease in the majority of developing countries is enormous. The active participation of many agencies will be required if change is to be achieved. Research on new forms of interventions and on more effective ways of delivering new or existing interventions is crucial. The cost of the process of evaluating a new intervention through clinical research can be very high; so high that it could not be covered by many developing countries without external support. In addition, many forms of interventions, especially new medicines and vaccines, may be very costly to manufacture or purchase. However, there are examples which show that, once an intervention, such as a medicine or a vaccine, has been shown to be effective, ways may be found of substantially reducing the costs of providing such an intervention to a developing country. Despite the great need for research to determine which forms of intervention in developing countries are most effective, the capacity of those countries to conduct relevant research is severely limited. Developing expertise in research to help countries to set their own priorities and to focus research on those priorities is a crucial obligation that sponsors of externally-funded research must acknowledge.

Setting priorities for research

- 10.8 Setting priorities for healthcare research is a particularly important issue in developing countries, because national resources for research are generally very limited. Clearly, the more a country can determine its own priorities and conduct its own research, the easier it will be to ensure that research proposed by external sponsors is appropriate and relevant to its national health needs. If there is no clear picture of the priorities for research related to healthcare within a country, it will be more difficult for government and external sponsors to collaborate in addressing them.
- 10.9 It follows that to enable effective collaboration with external sponsors, developing countries should have a mechanism allowing them to set priorities for research into healthcare, together with a robust mechanism for scientific review and ethical review of any proposed research (see Chapter 8). How this is managed will depend on the resources available in each country. **We therefore endorse the view of the Commission on Health Research for Development (1990) and its successor, the Task Force on Health Research for Development (1991) that all countries should set priorities for research into healthcare (paragraph 2.31).**

Failure to do so may mean that external sponsors wishing to conduct research will be unable to identify a country's crucial needs as regards research into healthcare and therefore may be more likely to propose inappropriate research with little relevance to the country in which it is conducted.

- 10.10 We do not take the view that all externally-sponsored research should fall within nationally defined priorities, since all research has the potential to contribute to the development of local skills and expertise, quite apart from the inherent value in diversity of research. However, there is a careful balance to be drawn. The inherent inequalities of power and advantage between developed and developing countries require that particular care is needed to restrain any tendency on the part of the sponsor to pursue their interests to the detriment of those of the host country. **We therefore recommend that when research funded by external sponsors is proposed which falls outside the national priorities for research into healthcare set by a host country, those proposing the research be required to justify the choice of the research topic to the appropriate research ethics committees in both the host and sponsoring countries (paragraph 2.32).**

Social and cultural issues

- 10.11 Systems of biomedical care in developed countries are generally based on common scientific assumptions. There are, however, a variety of other systems of diagnosis and healing which may vary a great deal across cultures and countries. This is particularly true of developing countries. Research into healthcare conducted along scientific lines in a particular society, or culture, will be affected by existing assumptions and practices. In any research in developing countries, therefore, these need to be addressed. Particular attention will need to be given to the means of informing potential participants about the proposed study and the process of seeking their consent. The differing conceptions of what respect for persons entails in many societies in the developing world, and the need for the community to discuss issues and reach agreement as a first step in the approval of a research project must be taken into account by researchers.
- 10.12 Research which pays no regard to the development of local infrastructures, or which fails to make appropriate use of local systems, skills and practitioners, may fail to maximise the benefit of the research to the community. The possibility and desirability of co-operation between practitioners of traditional medicines and scientific researchers on a particular research project should be considered on a case-by-case basis.

Ethical principles

- 10.13 The Working Party identified four ethical duties that are crucial in evaluating the actions and policies of individuals and organisations proposing to carry out research in developing countries. The four duties are the duty to alleviate suffering, to show respect for persons, to be sensitive to cultural differences, and the duty not to exploit the vulnerable. They constitute a framework for articulating the duties, obligations, claims and expectations of those involved in research related to healthcare. The practice of medicine is intrinsically justified by virtue of the duty to alleviate suffering. Research into healthcare makes an essential contribution to the alleviation of suffering. While the needs of our own communities may generally have the first claim on our resources, we have a duty to contribute to the alleviation of suffering elsewhere. Thus, there is an ethical imperative to conduct research, including that which addresses the health problems of developing countries.
- 10.14 The principle of respect for persons places important constraints on the performance of the duty to alleviate suffering. That duty, by itself, may lead us to the assumption that the less

suffering there is, the better the world is overall. However, the principle of respect for persons enjoins us to consider carefully the ways in which we seek to alleviate suffering. For example, policies which violate other interests of those involved, even if they offer the most straightforward way of reducing suffering, are to be weighed carefully.

- 10.15 An important characteristic of externally-sponsored research conducted in developing countries is that there are often cultural differences between those organising or funding the research and the researchers and participants in the host country. One potentially potent misuse of power is to be insensitive to the cultural perspectives that individuals bring to questions of health and healthcare. Indeed, the variety of beliefs and practices that exist may challenge the notions of overarching ethical principles. It may be claimed that the requirement to practice sensitivity to cultural differences leads to moral relativism, which is the view that different moral codes cannot be critically compared and evaluated. In our view, the existence of cultural diversity does not lead to moral relativism. Sensitivity to the values inherent in local practices does not require uncritical acceptance of them. What is required is a willingness to explore differences without prejudice and to seek as far as possible to understand them, informed by knowledge of local traditions and material circumstances.
- 10.16 We suggest that, as a matter of moral principle, the more powerful have a duty to refrain from exploiting to their own advantage the vulnerability of the weaker. Just as it is unacceptable that local political and economic elites should seek to pursue their own goals at the expense of populations participating in research, so it is unacceptable that researchers should select populations which are economically or politically weak and therefore vulnerable to exploitation, in order to test therapies more cheaply or in order to use the results for the benefit of other, more wealthy, communities.

The framework of guidance

- 10.17 The Working Party noted that an ethical inquiry does not concern itself only with the articulation of appropriate general values and principles; it has also to concern itself with the institutions and procedures through which these principles are put into practice. Researchers and sponsors who undertake research related to healthcare in developing countries are faced with difficult choices. On the one hand, they need to be sensitive to the local social and cultural context, while on the other they need to ensure that their clinical methods reflect the obligations imposed by the relevant national and international guidance. In practice, researchers and sponsors have been confronted with guidance which is often generalised and even contradictory. Nor has the guidance generally taken into account the special circumstances which characterise externally-sponsored research in developing countries.
- 10.18 The Working Party has concluded that training in interpreting and applying the guidance is an important accompaniment to the guidance itself. Unless guidance is clearly understood by researchers, sponsors and the members of the research ethics committees, it will be of little real value. So that a common understanding is established between researchers in both developing and developed countries, we suggest that education and training of those involved in biomedical research is undertaken so that the requirements of the guidance are clearly understood and implemented. **We conclude that in any revised or new guidance the provision of training in the ethical conduct of research should be a requirement placed on all involved in the sponsorship of research in developing countries (paragraph 5.26). We recommend that national and international sponsors of research, including government agencies and departments, charitable foundations and pharmaceutical companies, ensure that provision is made for education and training in the ethics**

of research of all of those professionals involved in research related to healthcare to ensure that the requirements of relevant guidance on ethics are met (paragraph 5.27). In addition, we encourage developing countries to take account of existing international and national guidance and to create national guidance for its clear and unambiguous application (paragraph 5.28).

Consent

- 10.19 The fundamental ethical duty of respect for persons requires that we do not act against a person's wishes, and thus genuine consent to participate in research must be obtained. For consent to be genuine, health professionals must do their best to communicate information accurately and in an understandable and appropriate way. The information provided to participants must be relevant, accurate and sufficient to enable a genuine choice to be made. It must include such matters as the nature and purpose of the research, the procedures involved and the potential risks and benefits.
- 10.20 An awareness of the social and cultural context in which research is to be conducted is required, so that communities and individuals can be informed of any aspect of the research that may cause them particular concern. The process of obtaining consent also needs to be designed to provide opportunities for participants to ask questions of personal interest about the proposed research.
- 10.21 In some circumstances there is a tension between the requirement that genuine consent to research be obtained, and cultural contexts in which giving certain information, such as a diagnosis of a serious disease to a patient, is not customary. The Working Party has considered these competing interests and has concluded that obtaining genuine consent to research from participants is vital in ensuring that respect for persons is promoted. Without appropriate information, participants in research may be harmed by being exposed to risks or dangers that they would prefer to avoid. In addition, they will be denied the opportunity to learn more about their condition, possible treatments, and any beneficial outcomes of the research. Consequently, when research is conducted in contexts in which information about diagnoses and options for treatment is not normally provided, care and sensitivity will be required to design appropriate consent procedures, so that participants receive appropriate information about research and genuine consent may be given.
- 10.22 For consent to be genuine, it must be freely given. In some societies it would be considered culturally inappropriate for researchers to ask individuals to participate in research without consulting the community or permission from community leaders. Three such situations can be distinguished: consultation is required with the community before individuals are approached about research; permission from a leader(s) of the community is required before any research is discussed with the community or individuals; the leader of the community is considered to have the authority to enrol participants in research. In each of these circumstances, to seek consent from an individual without seeking assent from leader(s) of the community, or creating public acceptance of research, may be considered disrespectful and may harm relationships within that community and between a community and researchers. We noted in Chapter 4 that we cannot avoid the responsibility of taking a view when the two aspects of respect – respect for culture and respect for persons – come into conflict with one another. We are of the view that the fundamental principle of respect for persons requires that participants who have the capacity to consent to research should never be subjected to research without such consent. The Working Party has concluded that assent from others may be necessary before research is conducted, but that it is not sufficient: individual participants must receive appropriate information about the research and be asked to give consent. To ensure that individual participants can make up their

own minds without undue communal pressure, anonymity for those who wish to decline to participate in research should be assured. **We recommend that, in circumstances where consent to research is required, genuine consent to participate in research must be obtained from each participant. In some cultural contexts it may be appropriate to obtain agreement from the community or assent from a senior family member before a prospective participant is approached. If a prospective participant does not wish to take part in research this must be respected. Researchers must not enrol such individuals and have a duty to facilitate their non-participation (paragraph 6.22).**

- 10.23 Participants in research may have a variety of motivations for taking part in research. The healthcare that a participant would receive as part of a research programme may amount to a significant inducement to take part. Researchers will need to be aware that when research is conducted in developing countries, prospective participants may have little or no alternative means of receiving healthcare for a condition, other than through the facilities supported by the research, and thus the healthcare provided as part of the research will amount to a significant inducement to participate. In addition, benefits unrelated to the research protocol, such as financial payments, may be offered to compensate for travel costs or time devoted to the research. The dividing line between acceptable and inappropriate inducements is a fine one. The larger an inducement, the more likely it is to be inappropriate, because it causes an individual to expose himself or herself to risks or potential harms that he or she would otherwise consider to be unacceptable. In addition, payments and other benefits unrelated to the research protocol will act as significantly greater inducements in developing countries than would similar amounts in more developed contexts. **We recommend that dialogue is needed with sponsors, external and local researchers and communities to ensure that any inducements to take part in research are appropriate to the local context, especially in circumstances where the research exposes participants to a risk of harm. Decisions about appropriate levels of inducement will need to be justified to local research ethics committees (paragraph 6.32).**
- 10.24 Concerns have been expressed that consent forms and information sheets used for research in developing countries may contain terms that are commonly used in the countries of those sponsoring the research but are inappropriate in the context in which the research is being conducted. Various forms of guidance give detailed indications of the matters about which participants should be informed.¹ It should always be remembered that such devices as information sheets and consent forms are intended to assist the consent process. Researchers will need to refer to the relevant guidance and consider which matters are relevant to their research and to the context in which the research is to be conducted, and how to express the information they seek to convey. Forms which are long, complex and inappropriate for the cultural context in which they are being used, are likely to confuse, rather than inform, participants in research, and should not be approved by research ethics committees.
- 10.25 There are circumstances in which, while genuine consent to research can be obtained, it may be inappropriate to ask participants in research to sign consent forms, no matter how well designed. One obvious example is when research is being conducted in an illiterate population. The Working Party considers that it is not consistent with the duty of respect for persons to require a prospective participant to 'sign' a written consent form that they are unable to read.

1 For example, Guideline 2 of the CIOMS 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects specifies 10 pieces of essential information which should be given to prospective research participants, including: the aims and methods of the research, the benefits that might reasonably be expected to result to the research participant or to others as an outcome of the research, any foreseeable risks or discomforts, the extent of the investigator's responsibility, if any, to provide medical services to the research participant, confidentiality of participant data and arrangements for compensation for research-related injuries.

In such circumstances other means of recording genuine consent to participate is required, to protect participants from being enrolled in research that they have not consented to. **Information sheets and consent forms must be designed to assist participants to make informed choices. We recommend that the information provided should be accurate, concise, clear, simple, specific to the proposed research and appropriate for the social and cultural context in which it is being given. Where it is inappropriate for consent to be recorded in writing, genuine consent must be obtained verbally. The process of obtaining consent and the accompanying documentation must be approved by a research ethics committee and, where only verbal consent to research is contemplated, include consideration of an appropriate process for witnessing the consent (paragraph 6.40).**

Standards of care

- 10.26 There has been significant international debate about the standards of care that should be provided to participants during externally-sponsored research in developing countries. In this Report, we have focused on the question of whether participants in the control group of a research trial should be provided with a universal standard of care, regardless of where the research is conducted. The different approaches that have been proposed when deciding the level of care that should be provided for those in the control group of a clinical trial can be divided into two broad categories:
- universal: the best treatment available anywhere in the world, wherever the research is conducted
 - non-universal: the treatment available in a defined region.
- 10.27 The Working Party is firmly of the view that the need to avoid exploitation is imperative. It is a fundamental ethical principle that those involved in research should not take advantage of the vulnerabilities created by poverty or a lack of infrastructure and resources. However, the Working Party considers that insisting upon a universal standard of care may not always be the best way to respect this principle.
- 10.28 At first sight, justice might seem to require that we treat people identically, regardless of context, because justice demands equal respect. If showing respect for the participants in a particular research project in the developed world demands that they receive a particular intervention, it would seem to follow that participants in similar research conducted in the developing world should receive the same intervention. To apply a lower standard of care would thus be not only to take advantage of the participants' vulnerabilities, but also to commit an additional wrong by perpetuating an injustice. However, the principle of equal respect does not imply that we must behave towards others in a uniform manner, since features of individuals and of their circumstances will differ. Parity of respect requires us to address the specific needs and circumstances of individuals in determining how to behave towards them. What we mean by equality is not that people must always be treated identically, but that 'for every difference in the way men are treated, a [relevant] reason should be given'.² Thus, equal respect for participants in research does not necessarily entail that they should receive equal treatment, regardless of where the research may be conducted. Instead, the circumstances in which the

2 See Williams B (1973) *The Idea of Equality*, in Williams B *Problems of the Self*, Cambridge University Press, New York, for a clear exposition of this point.

research will be conducted must be critically assessed to establish whether or not the variations in circumstances provide a morally relevant reason for offering a different standard of care.

10.29 We take the view that, in determining the appropriate standard of care to be provided to participants in the control group of a research trial, a number of factors should be considered by sponsors, researchers, and research ethics committees. These include:

- the appropriate research design(s) to answer the research question (in some situations only one research design may be appropriate to answer the research question, in others a number of research designs, in which different standards of care are offered to the control group, may be possible)
- the seriousness of the disease and the effect of proven treatments
- the existence of a universal standard of care for the disease or condition in question and the quality of the supporting evidence
- the standard(s) of care in the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can be afforded by the host and sponsoring country(ies) for the disease being studied
- the standard(s) of care which can effectively be delivered in the host country(ies) during research
- the standard(s) of care which can be provided in the host country(ies) on a sustainable basis.

10.30 Taking the above considerations into account, in some circumstances, it will be clear that a control group in a clinical trial should receive a universal standard of care, wherever they live. In contrast, there are situations in which it is clear that even if there were an agreed universal standard of care for a disease, it may not be possible for this standard to be provided to the control group in a research project. This may be because of practical considerations, for example because the country in which the research is to be conducted may not have the infrastructure to provide such treatment, or because research using such a standard of care would have little relevance to the country in which it is conducted. The decision about whether or not a universal standard of care should be provided to the control group is usually not straightforward and involves careful consideration of the factors outlined above.

10.31 Where it is not appropriate to require that a universal standard of care be provided to the control group in the light of all the relevant circumstances, questions arise about what standard of care should be provided. The ultimate goal of research must be to provide information about treatment and other interventions which can then be used by national governments to ensure that improvements are made in the provision of healthcare. Thus, for policy reasons, it seems sensible to take the particular country as the unit of focus, as it is national governments which, by and large, take responsibility for the health of their citizens and which make decisions about the provision of healthcare. With knowledge of the resources available to them, governments make decisions about the level of care which they can provide for the prevention and treatment of specific diseases or conditions. In that context, they set targets for the level of care that they will strive to achieve, often recognising that it will not be possible to meet this goal.

10.32 The Working Party is of the view that in externally-sponsored research, the level of care that ought be offered to participants should, as a minimum, be the standard that the country endeavours to provide nationally. In many circumstances, it may be appropriate for researchers to offer a higher level of care than this, while still conducting research that is relevant to the local setting.

- 10.33 We conclude that discussion with clinicians, researchers and representatives of government and health authorities within the host country is essential so as to establish what the best national level of treatment available as part of the national public health system is. **We recommend that in setting the standard of care for the control group of a particular research project the context in which the research is to be conducted be carefully evaluated. A suitable standard of care can only be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered to the control group is the best intervention available for that disease as part of the national public health system (paragraph 7.29).** In research that aims to improve current forms of treatment within a developing country it may be proposed that the standard of care to be provided to the control group is lower than the best available intervention as part of the host country's public health system. In exceptional circumstances such research may be justified (see paragraphs 7.30–7.31).
- 10.34 In some forms of research, such as those designed to determine the incidence of a disease in a population, or to prevent participants from contracting or developing a disease, the standard of care received by participants who develop the disease will not be immediately relevant to the research. Under these circumstances, however, there is still a need to consider the standard of care which a patient should receive because the disease, once diagnosed, may have serious implications for the individual. The issue was the subject of extensive consultation when the UNAIDS guidance on ethical considerations in research on a HIV preventive vaccine was drafted. **We endorse Guidance Point 16 of the UNAIDS guidance on Ethical Considerations in HIV Preventive Vaccine Research.³ We conclude that when research into preventive measures is conducted, wherever appropriate, participants who develop the disease being studied should be offered a universal standard of care for the disease under study. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered is the best available intervention as part of the national public health system for that disease (paragraph 7.33).**
- 10.35 During research into some diseases, participants may develop a condition that is related to the condition under study or an entirely unrelated condition. In some circumstances, it may be relatively easy for researchers to treat the condition or refer participants to a centre where treatment can be provided. In other cases, researchers may not have the expertise to treat the condition effectively and appropriate treatment may not be available locally as part of the public health system. This is a complex issue and decisions will need to be made on a case-by-case basis following discussion with clinicians, researchers and representatives of government and health authorities within the host country. **We recommend that before research begins, agreement should be reached about the standard of care that should be provided to participants in research who already have or who develop diseases other than the disease being studied. We conclude that the minimum standard of care that should be offered is the best intervention available as part of the national public health system. Any proposal which contemplates care of a lower standard must be justified to the relevant research ethics committees (paragraph 7.35).**

3 UNAIDS (2000) **Ethical Considerations in HIV Preventive Vaccine Research. UNAIDS Guidance Document.** Guidance Point 16: Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of the circumstances listed below. A comprehensive care package should be agreed upon through a host/community/sponsor dialogue, which reaches consensus prior to initiation of a trial, taking into consideration the following: level of care and treatment available in the sponsor country; highest level of care available in the host country; highest level of treatment available in the host country, including the availability of antiretroviral therapy outside the research context in the host country; availability of infrastructure to provide care and treatment in the context of research; and potential duration and sustainability of care and treatment for the trial participant.

Ethical review of research

- 10.36 The requirement that the ethics of research related to healthcare is subject to review is designed to protect participants in research. The Working Party considers that each proposal for externally-sponsored research in developing countries should receive three levels of assessment: relevance to priorities in healthcare within the country(ies); scientific validity; and ethical acceptability. While research ethics committees are not constituted to make decisions about whether or not the findings of research can be implemented within a country, they should, however, determine if the implications of possible research results have been discussed, including the possibility of ongoing provision of treatments shown to be successful. Research ethics committees must also be satisfied that appropriate scientific review of research has taken place. We accept that it is not possible to separate entirely the processes of reviewing the science and ethics of a research proposal, but as the two forms of review have quite different purposes we conclude that they should, where possible, be kept separate (paragraph 8.5). This may, but will not necessarily, require the establishment of separate committees.
- 10.37 We have outlined a number of issues which research ethics committees need to consider when reviewing externally-sponsored research. These include the appropriateness of procedures for giving information about the research to prospective participants and communities and recording consent; the standards of care that should be provided to participants in research and arrangements that have been made for post-trial access to interventions.
- 10.38 The mere presence of a research ethics committee in a country is not enough to ensure that research will be adequately reviewed. Committees may be ineffective for a variety of reasons, including a lack of financial and human resources, and a lack of training in, and experience of, ethical review. An effective system for ethical review is a crucial safeguard for participants in research. **We recommend that all developing countries should have in place a properly constituted and functioning system for the independent ethical review of research. This will include the establishment of effective research ethics committees.** Developing countries may determine that the most appropriate means of reviewing externally-sponsored research is via an independent national research ethics committee. **In such circumstances the establishment, funding and proper operation of independent national research ethics committees should be the responsibility of national governments. No research should be conducted without review at the national or local level (paragraph 8.16).**
- 10.39 In developing countries, research ethics committees may have access to only limited administrative or financial support. To meet the costs of effective review, some research ethics committees receive regular funding from government. Others levy fees for reviewing research protocols. Regardless of whether the financial support for research ethics committees comes from government, research institutions or as a result of levying fees for review, it is crucial that the independence of research ethics committees be maintained. **We conclude that there is a need for creative approaches to providing support, especially financial support, for research ethics committees, without compromising their independence. Sponsors should determine how they can meet the costs of ethical review without compromising the independence of the research ethics committee and should be responsible for meeting the costs of reviewing externally-sponsored research (paragraph 8.20).**
- 10.40 In order to ensure that acceptable ethical standards are observed in externally-sponsored research, research should be approved through a system of ethical review of research in both the host and the sponsoring country. As regards the latter, if a sponsor provides funding, it must

have the means of ensuring that the funds are being used in a manner that is ethically acceptable. However, the country in which the research is to be conducted must also be satisfied about the ethical acceptability of the research. **We recommend that externally-sponsored research projects should be subject to independent ethical review in the sponsor's country(ies) in addition to the country(ies) in which the research is to be conducted (paragraph 8.22).** Should there be disagreement between committees in the developed and developing country(ies), negotiation between the committees in the sponsor's country and the country in which the research is to be conducted may be required. There should be mechanisms available to facilitate such negotiation. Where there are irreconcilable differences between research ethics committees, a committee may choose not to approve the research.

- 10.41 For research ethics committees to function effectively, committee members must receive adequate training. A number of national and international programmes are being established to develop expertise in ethical review in developing countries. Concerns have been expressed that training programmes for members of research ethics committees in developing countries, sponsored by a single developed country, may tend to reflect the views and procedures of the sponsoring country. **We recommend that international programmes and organisations, including the World Health Organization (WHO), continue to expand their current programmes for establishing, training and monitoring the development of research ethics committees. Funding should be provided to these international programmes for such purposes by bodies that sponsor research in developing countries (paragraph 8.29).**

What happens once research is over?

- 10.42 Once an externally-sponsored research study is completed in a developing country, the researchers and their sponsors are confronted with a number of issues relating to the future provision of healthcare benefits to the participants in the research and to the wider community. Many have taken the view that to fail to provide treatment which has been shown to be successful to the participants in research is ethically unacceptable. We take the view that in general, it is the responsibility of governments and not researchers or sponsors to determine the level of healthcare and the range of treatments and medicines that are provided to populations. However, researchers and sponsors often directly contribute to the strengthening of local healthcare facilities, so as to facilitate the research and to act as an inducement to individuals to participate. In addition, researchers may and frequently do act as advocates for the adoption of a medicine or vaccine shown to be successful. We recognise that sponsors are rarely in a position to agree to open-ended commitments once the research is completed, whether for the maintenance of facilities for healthcare or for the provision of interventions, but these are issues that need to be discussed and agreed by the research ethics committee, to the extent possible, before the research is initiated.
- 10.43 In externally-sponsored research, a valuable contribution can be made towards the development of local expertise during the research, so that there is the potential for continued improvement in healthcare once the research is complete. **We endorse the Council of International Organisations of Medical Sciences (CIOMS) Guidelines (1993) (Guideline 15) and recommend that sponsors of research should require that the development of local expertise in healthcare is an integral component of research proposals. Consideration should be given to the extent to which any strengthening of local healthcare facilities can be done in such a way that the changes are sustainable in the local context once the research is over (paragraph 9.12).**

- 10.44 With regard to the provision of an intervention shown to be successful once the research is completed, there are three groups of people to be considered: members of the control group in a trial, all of the participants in the research project, and the wider community in which the research took place.
- 10.45 The principle that those in the control arm of a trial should be provided with the intervention when it has been demonstrated to be efficacious is widely acknowledged. We consider that there is an ethical obligation to provide a control group with an intervention when it would benefit them (paragraph 9.24). **We conclude moreover that it would not be ethically acceptable for any study to begin without a decision having been made about whether or not those in control groups will be offered an intervention shown to be successful on completion of the trial, where relevant and appropriate. Participants should be informed of the decision as part of the process of obtaining their consent (paragraph 9.27).**
- 10.46 Participants in research may have conditions that require ongoing treatment. In such cases, it may be suggested that there is an obligation to continue to provide an intervention that has been shown to be effective to all participants. While such a requirement would be commendably aspirational, it may not be possible, especially in relation to ongoing treatment for chronic diseases. **We therefore endorse the US National Bioethics Advisory Commission (NBAC) recommendation that researchers should endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee (paragraph 9.31).**⁴
- 10.47 The most contentious issue concerning the future provision of benefits arising from research related to healthcare is the availability of successful interventions to the wider community once research is over. The Working Party acknowledges that if sponsors were required to fund the future provision of effective interventions, the majority would no longer support such research. Provision of a successful intervention to the wider community is primarily the responsibility of governments. However, there have been significant contributions from the pharmaceutical industry, although these are, by necessity, seldom open-ended. We have concluded that the complexity of the circumstances relating to the availability of interventions after the completion of a trial makes it difficult to formulate general guidance which applies to different forms of interventions. The need for further research, the role for research relating to the local delivery of interventions, the change in the cost of medicines, the existing framework for healthcare, and the commitment of policy-makers, are all factors which will influence the availability of a successful intervention. Despite these uncertainties, we conclude that there is a duty on researchers to address the issue before any research is initiated.
- 10.48 **We recommend that the following issues are clearly considered by researchers, sponsors, national healthcare authorities, international agencies and research ethics committees as part of any research protocol before research relating to healthcare involving the testing of new interventions is undertaken:**
- **the need, where appropriate, to monitor possible long-term deleterious outcomes arising from the research, for an agreed period of time beyond the completion of the research**
 - **the possibility of providing participants with the intervention shown to be best (if they are still able to benefit from it), for an agreed period of time**

4 National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research**: Recommendation 4.1.

- **the possibility of introducing and maintaining the availability to the wider community of treatment shown to be successful (paragraph 9.48).**⁵
- 10.49 **We endorse the NBAC recommendation that research proposals submitted to those committees should include an explanation of how new proven interventions could be made available to some or all of the host country population and that investigators should justify to the relevant research ethics committee why the research should be carried out if this is not thought possible (paragraph 9.49).**⁶
- 10.50 Despite the very great need for healthcare research in developing countries, local expertise in research tends to be severely limited. It is therefore particularly important that sponsors of research promote genuine partnerships between researchers in developed and developing countries when research is externally sponsored in order to strengthen expertise in research and maximise the opportunity for the transfer of knowledge and skills. **We recommend that external sponsors of research should require that the development of expertise in research be an integral component of all research in developing countries. Consideration should also be given to the development and support of expertise so that equipment obtained for the purposes of a research project can continue to be used and maintained (paragraph 9.52).**

Concluding comments: a framework for future action

- 10.51 In this Report, we have set out an ethical framework for assessing the duties and responsibilities of those involved in designing and conducting research related to healthcare. The framework is based on four principles: the duty to alleviate suffering; the duty to show respect for persons; the duty to be sensitive to cultural differences and the duty not to exploit the vulnerable. Rather than formulating a strict prescription of conduct which these principles would require when research in developing countries is externally sponsored (such as stipulating that a universal standard of care be provided), we have emphasised the critical importance of taking social, cultural and economic contexts into account when applying these principles, and have identified the minimum requirements which must be met in all circumstances. Particular care is required in those countries which do not have well established procedures for the protection of participants in research.
- 10.52 We are aware that researchers, sponsors and others who are involved in research related to healthcare are faced with diverse and sometimes conflicting guidance. Our contribution therefore has been to present an ethical framework as a guide for others to use when determining how to apply the guidance. In particular, the development of national guidance and the strengthening of the process of ethical review of research are priorities for developing countries which will afford a further layer of protection to participants in research.
- 10.53 In this Report we have argued for approaches to consent, standards of care, ethical review and the future provision of healthcare that take into account not only the need to protect participants in research, but also the economic realities that are faced by the majority of developing countries. In doing this, it is crucial that the recommendations in this Report are taken as a whole. Thus, the flexibility in tailoring standards of care and procedures for obtaining consent for specific research projects must be accompanied by the development of a rigorous and effective process of ethical review that assesses the appropriateness of the proposed research. This will allow research to be designed so that it has the greatest chance of providing relevant information about a population and thus alleviating suffering, without risking exploitation of vulnerable communities.

⁵ This consideration is especially important for expensive interventions.

⁶ National Bioethics Advisory Commission (2001) **Ethical and Policy Issues in International Research: Recommendation 4.2.**

144 หน้าว่าง



*Guidance on research
related to healthcare*

Appendix 1

146 หน้าว่าง



Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI¹

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, 'The health of my patient will be my first consideration,' and the International Code of Medical Ethics declares that, 'A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.'
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

¹ Reproduced with permission from the World Medical Association.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of

the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

NOTE OF CLARIFICATION ON PARAGRAPH 29 OF THE WMA DECLARATION OF HELSINKI

The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

National guidance on research related to healthcare

Table 1

Examples of national guidance on research related to healthcare

Year	Source	Title
1979	US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research	The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research
1986	Royal College of Physicians (RCP), UK	Research Involving Healthy Volunteers
1988	Regulation, France	Law No. 88-1138 on the Protection of Persons agreeing to Biomedical Research ('Huriet Law')
1990	RCP, UK	Research Involving Patients
1991	Regulation, US	Code of Federal Regulations Title 45 Public Welfare Part 46 Protection of Human Subjects
1991	National Health and Medical Research Council (NHMRC), Australia	Guidelines on Ethical Matters in Aboriginal and Torres Strait Islander Health Research

Table 1*Continued*

Year	Source	Title
1992	Regulation, Finland	The Patient Rights Act (785/1992)
1992	Medical Research Council (MRC), UK	Responsibility in Investigations on Human Participants and Material and on Personal Information
1993	Medical Research Council of South Africa	Guidelines on Ethics for Medical Research (3rd edition)
1995	Ministry of Public Health, Thailand	Rule of the Medical Council on the Observance of Medical Ethics
1996	National Health Council of Brazil	Resolution No. 196/96 on Research Involving Human Subjects
1997	Health Research Council of New Zealand	Guidelines on Ethics in Health Research
1997	Medical Research Council of Canada	Code of Ethical Conduct for Research Involving Humans
1997	National Consensus Conference on Bioethics and Health Research in Uganda	Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda
1998	Committee on Research involving Human Subjects, China	Guidelines on Ethical Review of Medical Research
1998	Legislation, The Netherlands	Law of 26 February 1998, containing regulations with regard to medical-scientific research on humans
1998	MRC, UK	Good Clinical Practice in Clinical Trials
1998	MRC, UK	Interim Guidelines. Research Involving Human Participants in Developing Societies. Ethical Guidelines for MRC-sponsored Studies
1998	Health Research Council of New Zealand	Guidelines for Researchers on Health Research Involving Maori
1998	Medical Research Council of Canada/ National Sciences and Engineering Research Council of Canada/Social Sciences and Humanities Research Council of Canada	Tri-Council Policy Statement. Ethical Conduct for Research Involving Humans
1999	Regulation, Finland	Decree on Medical Research (986/1999)
1999	NHMRC, Australia	National Statement on Ethical Conduct in Research Involving Humans
2000	Indian Council of Medical Research	Ethical Guidelines for Biomedical Research on Human Subjects
2000	Nepal Health Research Council	Ethical Guidelines for Biomedical Research Involving Human Participants in Nepal
2000	Clinical Trials Working Group of the South African Department of Health	Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa
2001	National Committee for Ethics in Social Research in Health (NCESSRH) India	Ethical Guidelines for Social Science Research in Health
	Food and Drug Administration (US)	21 CFR 50: Protection of Human Subjects
	Food and Drug Administration (US)	21 CFR 56: Institutional Review Boards
	Agency for International Development (US)	22 CFR 225: Protection of Human Subjects

National and international guidance on specific topics in research related to healthcare

Table 2

Examples of national guidance on standards of care

Source	Country	Text
National Health Council of Brazil 'Resolution No 196/96 on Research Involving Human Subjects' (1996)	Brazil	'... the use of placebos, in terms of non-maleficence and of methodological requirement [must be fully justified] ...' III.3 f
Indian Council of Medical Research 'Ethical Guidelines for Biomedical Research on Human Subjects' (2000)	India	'Denial of the available treatment to control (placebo) group of patients is unethical.' p. 27. The use of a placebo as one arm of a trial in experimental epidemiological studies is not prohibited however. See p. 35
Clinical Trials Working Group of the South African Department of Health 'Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa' (2000)	South Africa	'It may be justifiable to use a placebo in communities that do not have access to interventions that are the standard care in resource-rich settings.' however '... the balance between potential harms and benefits should be such that the potential benefits to the community would considerably outweigh the harm.' Paragraph 9.3.2 'During and after a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values ... a subject [should be informed] when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.' Paragraph 3.4
National Consensus Conference on Bioethics and Health Research in Uganda 'Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda' (1997)	Uganda	'The investigator must provide adequate and safe medical ... care, where appropriate, to participants during the clinical trial ... and must ensure that appropriate medical care and follow-up procedures are maintained after the trial for a period of time that is dependent upon the nature of the disease, the trial and the intervention(s).' V Procedures for the Investigation of New Drugs and Devices, D. Responsibilities of the Investigator, (3), p. 53 'Placebo-controlled trials may be conducted (a) [where] based on knowledge ... available at the commencement of the trial, the new drug or device to be tested does not confer any significant benefit compared to the placebo, and (b) the placebo arm is provided with the treatment or diagnosis product or device considered to be the normal standard of care in the community in which the trial is being conducted'. V Procedures for the Investigation of New Drugs and Devices, C. Justification of the Trials, (3) (a) and (b), p. 52
Medical Research Council 'Interim Guidelines for Research Involving Human Participants in Developing societies – Ethical Guidelines for MRC-sponsored studies' (1998)	UK	Requires that the 'best proven ... method ... should take account of the available and feasible healthcare in the particular developing society'. Specific considerations: Paragraph 6
Royal College of Physicians 'Research involving Patients' (1990)	UK	'Where ... effective treatment is important for the future well being of the patient, ... a controlled trial [should] ... be undertaken only if, at the outset, the investigator does not know whether the trial treatment is more effective or less effective than the standard treatment with which it is to be compared ...' Paragraph 7.99 However, 'Withholding effective treatment for a short time, whether or not it is substituted by a placebo, can sometimes be acceptable in order to validate a technique of measurement or confirm the sensitivity or discrimination of a therapeutic trial design.' Paragraph 7.100

Table 2*Continued*

Source	Country	Text
National Bioethics Advisory Commission 'Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries' (2001)	US	'Researchers and sponsors should design clinical trials that provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country. Any study that would not provide the control group with an established effective treatment should include a justification for using an alternative design. Ethics review committees must assess the justification provided, including the risks to participants, and the overall ethical acceptability of the research design.' Recommendation 2.2

Table 3**Examples of national and international guidance on responsibilities for harm caused by research**

Source	Country	Text
CIOMS 'International Guidelines for Ethical Review of Epidemiological Studies' (1991)	International	'Some epidemiological studies may inadvertently cause harm. Monetary losses should be promptly repaid. Compensation is difficult when it is not appropriate to make monetary payments. Breach of confidentiality or insensitive publication of study findings, leading to loss of group prestige, or to indignity, may be difficult to remedy. When harm results from a study, the body that has sponsored or endorsed the study should be prepared to make good the injury, by public apology or reparation.' Paragraph 47
CIOMS 'International Ethical Guidelines for Biomedical Research Involving Human Participants' (1993)	International	'Research subjects who suffer physical injury as a result of their participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability. In the case of death their dependants are entitled to material compensation. The right to compensation may not be waived.' Guideline 13
National Health Council of Brazil 'Resolution N° 196/96 on Research Involving Human Subjects' (1996)	Brazil	'The researcher, the sponsor and the institution must assume full responsibility for providing comprehensive care to the research subjects, as regards complications and injury resulting from foreseen risks.' Paragraph V.5 'Research subjects that suffer any type of injury resulting from their participation in the research, regardless of such injury having been foreseen in the terms of consent, or not, have the right to receive comprehensive medical care, as well as an indemnity.' Paragraph V.6 'Under no circumstance will the research subject be required to waive his/her right to indemnity for injury resulting from the research. The form used in obtaining the freely given and informed consent of the research subjects must not contain any clause exempting the researcher from responsibility or depriving any individual of his/her legal rights, including the right to seek an indemnity for injury resulting from the research.' Paragraph V.7
Indian Council of Medical Research 'Ethical Guidelines for Biomedical Research on Human Subjects' (2000)	India	'Each research shall include an in-built mechanism for compensation for the human subjects either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive after-care, including treatment during and after the research or experiment, in respect of any effect that the conduct of research or experimentation may have on the human subject and to ensure that immediate recompense and rehabilitative measures are taken in respect of all affected, if and when necessary.' P. 9

Table 3

Continued

Source	Country	Text
National Consensus Conference on Bioethics and Health Research in Uganda 'Guidelines for the Conduct of Health Research involving Human Subjects in Uganda' (1997)	Uganda	'The investigator must provide evidence of insurance to cover claims for injuries, disabilities, or death of a clinical trial participant that has resulted from participation in a clinical trial.' V. D. (6) 'The sponsor is responsible for providing compensation or indemnity in the event of trial-related serious injury, disability, or death, according to laws and regulations in effect at the time of the trial.' V. E. (6)
Royal College of Physicians 'Research Involving Patients' (1990)	UK	'Although the chances of harm coming to patients in the course of carefully conducted research are very small, it is important that proper arrangements are made to compensate patients in the event of such harm occurring.' Recommendation 58 'Bodies that sponsor research, including both publicly funded bodies ... and the pharmaceutical industry, should now so arrange their affairs as to implement the principle that injury due to participation in research sponsored by them or conducted by their staff with the approval of a Research Ethics Committee shall be compensated by a simple, informal and expeditious procedure.' Recommendation 59 'In the event of any significant injury the patient must be entitled to receive compensation regardless of whether there may or may not have been negligence or legal liability on any other basis.' Recommendation 60
National Bioethics Advisory Commission 'Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries' (2001)	US	'The U.S. government should not sponsor or conduct clinical trials that do not, at a minimum, provide the following ethical protections... adequate care of and compensation to participants for injuries directly sustained during research ...' Recommendation 1.1

Table 4

Examples of national and international guidance on the composition of research ethics committees

Source	Country	Text
CIOMS 'International Guidelines for Ethical Review of Epidemiological Studies' (1991)	International	Epidemiologists, other health practitioners and lay persons qualified to represent a range of community, cultural and moral values. Membership should be of diverse composition and include representatives of any populations specifically targeted for study. Paragraph 36
CPMP/ICH 'International Conference on Harmonisation (ICH) Note for Guidance on Good Clinical Practice' (1996)	International	At least one member should be a non-scientist and one member independent of the institution/trial site. Paragraph 3.2.1
United Nations Development Programme (UNDP), World Bank, World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR) 'Operational Guidelines for Ethics Committees that Review Biomedical Research' (2000)	International	Should be multidisciplinary and multi-sectorial in composition, including relevant scientific expertise, balanced age and gender distribution, and laypersons representing the interests and the concerns of the community. Paragraph 4

Table 4*Continued*

Source	Country	Text
Indian Council of Medical Research 'Ethical Guidelines for Biomedical Research on Human Subjects' (2000)	India	Chair should not be head of the institution and preferably drawn from outside the institution. Members should include a mix of medical and non-medical, scientific and non-scientific individuals and representatives of the lay public. The ethical committee at any institution can have as its members, individuals from other institutions or communities if required. Diversity is important in terms of age, gender, community, etc. Members should be aware of local, social and cultural norms. Based on the nature of the research proposals, subject experts could be selected, along with specific patient groups as appropriate. Model membership would include: the Chair, 1-2 basic medical scientists, 1-2 clinicians from various Institutes, 1 legal expert or retired judge, 1 social scientist or NGO representative, 1 philosopher/ ethicist/ theologian, 1 lay person from the community and a Member Secretary. P. 12–13
South Africa Department of Health 'Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa' (2000)	South Africa	Members should be representative of the communities they serve and reflect the demographic profile of the population of South Africa. Both genders should be represented with no more than 70% of members coming from one of the genders. Membership should include at least one of each of the following: lay member, legally trained member, member with knowledge of, and current experience in areas of research that are regularly considered by the ethics committee, member with knowledge of and current experience in the professional care. counselling or treatment of people. Paragraph 8.2
National Consensus Conference on Bioethics and Health Research in Uganda 'Guidelines for the Conduct of Health Research involving Human Subjects in Uganda'(1997)	Uganda	Members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. Diversity should be demonstrated in terms of gender, region, religion and cultural backgrounds and sensitivity to issues such as community attitudes. Membership should allow for the acceptability of the proposed research to be ascertained in terms of institutional commitments and regulations, applicable law and standards of professional conduct and practice. Both sexes should be represented. The Committee must not consist entirely of members from one profession, tribe, religion or social or economic class and lack of formal education should not exclude an individual from membership. Membership should include at least one of the following however: member whose primary concerns are in scientific areas, member whose primary concerns are in non-scientific areas, member unaffiliated with the institution and not from the immediate family of a person affiliated with the institution. 11. A. 1–4
Department of Health 'Ethics Committee Review of Multi-centre Research. Establishment of Multi-Centre Research Ethics Committees' (1997)	UK	Diverse composition reflecting a mix of gender, age and ethnic background and drawn from throughout the region the MREC serves. Membership should include: hospital medical staff, nursing staff, general practitioners, other NHS professional staff and lay persons. Health professionals should be mainly drawn from those actively involved in clinical care and those experienced in clinical investigation and research. Paragraph 11

Table 4

continued

Source	Country	Text
Department of Health 'Governance Arrangements for NHS Research Ethics Committees' (2001)	UK	Membership should consist of a mixture of 'expert' and 'lay' members, balanced in terms of age and gender and with ethnic minorities and the disabled represented. Expert members should have relevant methodological and ethical expertise, experience of clinical practice, statistics relevant to research or pharmacy. At least one third of membership should be comprised of lay members who are independent of the NHS. At least half of the lay membership should consist of persons who have never been either health or social care professionals or involved in carrying out research involving human participants, their tissue or data. Advice may be sought from specialist referees on relevant aspects of a research proposal where such lies beyond the expertise of the existing members. Paragraphs 6.2–6.5, 6.7, 6.10

Table 5

Examples of national guidance on what should be provided once research is over

Source	Country	Text
National Health Council of Brazil 'Resolution No. 196/96 on Research Involving Human Subjects' (1996)	Brazil	Research involving human subjects, must whenever possible guarantee that: 'research in communities is translated into benefits whose effects continue to be felt after the research is concluded.' '... the individuals and communities where the research was undertaken [receive] a return on the benefits obtained in the research. When it is really beneficial to foster or encourage changes in practices or behaviors in the interest of a community, the research protocol must include, whenever possible, provisions to communicate such benefits to the individuals and/or communities' 'to ensure the research subjects the benefits resulting from the research project, in terms of social return, access to procedures, products or research agents' 'to submit evidence, in case of research conducted abroad or with external cooperation, of commitments and advantages to the research subjects and to Brazil, which will result from the implementation of the research... Studies sponsored by external organizations must also respond to training needs in Brazil, so that the country be able to independently develop similar projects.' Paragraph III.3m,n,p,s
Indian Council of Medical Research 'Ethical Guidelines for Biomedical Research on Human Subjects' (2000)	India	'After the clinical trial is over, if need be, it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in the country.' P. 27
Clinical Trials Working Group of the South African Department of Health 'Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa' (2000)	South Africa	'Where a patient has a therapeutic response to a study drug, that patient should be offered ongoing treatment. In designing studies, consideration should be given to the costs of long term provision of study drugs and of clinical monitoring, including the costs of medical staff.' Paragraph 9.3.5 'Research, which has direct public health implications, such as vaccine trials, require wide consultation. This should include discussions with South African Department of Health and the Medical Research Council so that implementation of study results can be addressed at an early stage.' Paragraph 9.7.3

Table 5*Continued*

Source	Country	Text
National Consensus Conference on Bioethics and Health Research in Uganda 'Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda' (1997)	Uganda	'The investigator must provide assurances that, if the investigational product is found to be beneficial, the investigator will make every effort to ensure its provision, without charge, to participants in the trial following the conclusion of the trial. In addition, the investigator shall make a reasonable effort to secure the product's availability to the local community in which the research occurred.' V.D.(4)
MRC 'Guidelines for Good Clinical Practice in Clinical Trials' (1998)	UK	'The [Trial Steering Committee] should ensure that appropriate efforts are made to ensure that the results of the trial are adequately disseminated and due consideration is given to the implementation of the results into clinical practice.' Paragraph 6.9.1
NBAC 'Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries' (2001)	US	'Researchers and sponsors in clinical trials should make reasonable, good faith efforts before the initiation of a trial to secure, at its conclusion, continued access for all participants to needed experimental interventions that have been proven effective for the participants. Although the details of the arrangements will depend on a number of factors (including but not limited to the results of a trial), research protocols should typically describe the duration, extent, and financing of such continued access. When no arrangements have been negotiated, the researcher should justify to the ethics review committee why this is the case.' Recommendation 4.1 'Whenever possible, preceding the start of research, agreements should be negotiated by the relevant parties to make the effective intervention or other research benefits available to the host country after the study is completed.' Recommendation 4.2 'Where applicable, U.S. sponsors and researchers should develop and implement strategies that assist in building local capacity for designing, reviewing, and conducting clinical trials in developing countries. Projects should specify plans for including or identifying funds or other resources necessary for building such capacity.' Recommendation 5.6

Guidance on the ethics of research related to healthcare available via the internet

International and regional guidance

CIOMS (1993) **International Ethical Guidelines for Biomedical Research Involving Human Subjects**

Available at: http://www.cioms.ch/frame_1993_texts_of_guidelines.htm

CIOMS (1991) **International Guidelines for Ethical Review of Epidemiological Studies**

Available at: http://www.cioms.ch/frame_1991_texts_of_guidelines.htm

Council of Europe (1997) **Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine**

Available at: <http://conventions.coe.int/treaty/en/treaties/html/164.htm>

CPMP/ICH (1996) **Note for Guidance on Good Clinical Practice**

Available at: <http://www.emea.eu.int/pdfs/human/ich/013595en.pdf>



UNAIDS (2000) **Ethical considerations in HIV preventive vaccine research. UNAIDS guidance document**

Available at: www.unaids.org/publications/documents/vaccines/vaccines/Ethicsresearch.pdf

WHO (1995) **Guidelines for good clinical practice (GCP) for trials on pharmaceutical products**

Available at: <http://www.who.int/medicines/library/par/ggcp/GCPGuidePharmatrials.pdf>

WHO (2000) **Operational Guidelines for Ethics Committees that Review Biomedical Research**

Available at: www.who.int/tdr/publications/publications/ethics.htm

WMA (2000) **Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000**

Available at: http://www.wma.net/e/policy/17-c_e.html

National guidance

Agency for International Development (US) **22 CFR 225: Protection of Human Subjects**

Available at: http://www.access.gpo.gov/nara/cfr/waisidx_99/22cfr225_99.html

Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks **Code of Federal Regulations Title 45 Part 46: Protection of Human Subjects**

Available at: <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

Food and Drug Administration (FDA) (US) **21 CFR 50: Protection of Human Subjects**

Available at: http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr50_00.html

Food and Drug Administration (FDA) (US) **21 CFR 56: Institutional Review Boards**

Available at: http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr56_00.html

Food and Drug Administration (FDA) (US) **21 CFR 312: Investigational New Drug Application**

Available at: http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr312_99.html

Health Research Council of New Zealand (1997) **HRC Guidelines on Ethics in Health Research**

Available at: <http://www.hrc.govt.nz/ethicgui.htm>

Indian Council of Medical Research (2000) **Ethical Guidelines for Biomedical Research on Human Subjects**

Available at: <http://www.icmr.nic.in/ethical.pdf>

Health Research Council of New Zealand (HRC) (1998) **Guidelines for Researchers on Health Research Involving Maori**

Available at: <http://www.hrc.govt.nz/Maoguide.htm>

Medical Research Council (MRC) (UK) (1998) **Guidelines for Good Clinical Practice in Clinical Trials**

Available at: <http://www.mrc.ac.uk/pdf-ctg.pdf>

Medical Research Council (MRC) (UK) (2000) **Personal Information in Medical Research**

Available at: <http://www.mrc.ac.uk/pdf-pimr.pdf>

Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada (1998) **Tri-Council Policy Statement. Ethical Conduct for Research involving Humans**

Available at: <http://www.nserc.ca/programs/ethics/english/ethics-e.pdf>

Medical Research Council (South Africa) (1993) **Guidelines on Ethics for Medical Research, 3rd Edition**

Available at: <http://www.mrc.ac.za/ethics/ethics.htm>

(A 4th edition is being prepared and will be made available at: <http://www.sahealthinfo.org/ethics/index.htm>)

National Bioethics Advisory Commission (US) (2001) **Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries**

- Volume I: Report and Recommendations of the National Bioethics Advisory Commission
- Volume II: Commissioned Papers

Available at: <http://bioethics.georgetown.edu/nbac/pubs.html>

National Health and Medical Research Council of Australia (1991) **Guidelines on Ethical Matters in Aboriginal and Torres Strait Islander Health Research**

Available at: <http://www.health.gov.au/nhmrc/issues/asti.pdf>

National Health and Medical Research Council of Australia (1999) **National Statement on Ethical Conduct in Research Involving Humans**

Available at: <http://www.health.gov.au/nhmrc/publications/pdf/e35.pdf>

National Health Council of Brazil (1996) **Resolution No. 196/96 on Research Involving Human Subjects**

Available at: http://www.aids.gov.br/resolution_196.htm

National Health Council of Brazil (1997) **Resolution No. 251/1997**

Available at: conselho.saude.gov.br/docs/CNS.Reso251.English.doc

National Health Council of Brazil (1999) **Resolution No. 292/1999**

Available at: conselho.saude.gov.br/docs/CNS.Reso292.English.doc

South African Department of Health (2000) **Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa**

Available at: <ftp://ftp.hst.org.za/pubs/govdocs/clinical.pdf>

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (US) (1979) **The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research**

Available at: <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>

160 หน้าว่าง



*Types of research
design*

Appendix 2

162 หน้าว่าง



Many different kinds of research related to healthcare take place in developing countries. These include:

- basic research
- clinical research
- epidemiological research
- social and behavioural research
- intervention studies, including clinical trials and community-based trials
- health services and operational research

Basic research is usually laboratory-based and includes studies at the cellular level, and of immunity and pathogenesis. Such research is often dependent on the use of samples from patients.

Clinical research is often conducted with patients in a medical setting, such as a hospital, and is designed to obtain better information on the natural history or pathogenesis of a condition that may lead to improved strategies for diagnosis, treatment or prevention of a disease.

Epidemiological research usually involves population-based investigations, which may be cross-sectional surveys of selected populations (case-control studies) or all members of a community, or may involve longitudinal study of a population over time (cohort studies). Such research is conducted to obtain an improved understanding of the natural history of a disease or to identify factors that increase or decrease the risk of disease in individuals. Often such investigations involve the study of large populations and they may be observational or interventional in nature. The aim is to identify strategies for the better prevention or treatment of disease, through an improved understanding of risk factors for disease or for progression of disease.

Social and behavioural research is often a component of epidemiological research and focuses on the study of behavioural and social factors that may modify risk of disease in individuals or in populations. Such research may involve the collection of sensitive information about a person and their lifestyle (e.g. sexual behaviour). While some forms of research may only involve observation others may involve studying or testing ways of changing behaviour or social circumstances.

Intervention studies are conducted to evaluate the impact of specific interventions on the prevention of disease, often in the context of community-based intervention trials, or in modifying the clinical course of disease, often in the context of clinical trials. Such research may provide the basis for policy decisions and priority setting. Intervention studies usually involve the comparison of different treatment or prevention strategies in which the current intervention method is compared with another method, often new, that may be more efficacious than the existing intervention. If there is no existing effective intervention, a placebo or 'no intervention' may be used as the comparison against which to assess the impact of the new intervention. Ideally, individuals are randomly allocated to receive the different interventions being compared in the trial.

Health services and operational research are concerned with the study of methods of delivery of healthcare, access to treatment and quality of care, with the aim of finding improved methods that lead to better care. Such studies often include an evaluation of the cost of providing the intervention and the benefit it provides.

164 หน้าว่าง



*Issues to be considered
when reviewing
research proposals*

166 หน้าว่าง



Policy issues

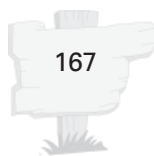
- Does the research need to be conducted in the particular country under consideration?
- Can the purpose of the research be justified? Is the proposed research relevant to national priorities for healthcare-related research? If the research is not relevant to the national priorities, is it nevertheless justified?
- Have the criteria for selecting the study population been outlined? Have any issues related to the gender of the study population been considered?
- Is the funding which has been allocated sufficient to complete the project?
- If favourable, could the results be implemented, either now or in the foreseeable future? If not, does the research have any beneficial secondary or indirect effects (e.g. the development of expertise in research)?

Scientific issues

- Is the researcher undertaking the research appropriately qualified and does he or she have the relevant experience?
- Is the researcher available for the duration of the study?
- Are the staff supporting the research and the facilities available, including technical facilities, adequate?
- Is this the first time this type of research has been conducted? If not, has the scientific value of undertaking the research been justified?
- Is the research design appropriate? Is it likely to yield an unambiguous answer to the research questions which have been posed?
- Is it possible for the quality control of data and analysis to be achieved?
- Has consideration been given to issues associated with biosafety and good manufacturing practice?
- Can the diagnostic, therapeutic and preventative interventions be handled safely?
- Is a control group being used in the research? If so, have details been included in the proposal of the treatment that will be given?
- Will there be any form of follow-up for participants in research? If so, have details of this been provided?

Ethical issues

- Has the research received appropriate scientific review?
- Has the project been given approval by an ethics review committee in the host/sponsoring country?
- Have any efforts been made to consult with the relevant communities during the course of designing the research?



- Have details been given of the measures to be used to recruit prospective participants in research?
- Has consideration been given to who will benefit from the research?
- Has consideration been given to the risks involved in undertaking the research? Have measures been taken to minimise risks to participants? Is there adequate provision for monitoring the data collected to ensure the safety of subjects?
- Have details been given of the information that will be made available to prospective participants? Is this appropriate and complete? Is it in a language and at a level of complexity appropriate to prospective participants in research?
- Have details been given of the procedure that will be used to obtain assent at the level of institutions and communities, where appropriate?
- Have details been given of the procedure that will be used to obtain consent from individual participants? Is it appropriate to ask participants to sign a consent form? If not, how will their consent be recorded? Where verbal consent to research is anticipated, is there an appropriate process for witnessing the consent?
- Have provisions been made for receiving and responding to queries and complaints from participants in research or their representatives during the course of a research project?
- Have details been given of who will be given access to the personal data of the participants in research, including medical records and biological samples? Are measures being put in place to maintain confidentiality and are these adequate?
- Are the standards of care being proposed acceptable? Are they appropriate for the country in which the research is being conducted?
- Are there other research designs which could answer the research question being posed? If so, why has this particular design been proposed?
- Is a control arm to be used? If so, has its use been properly justified? If it is being proposed that the control group in the research should receive less than a universal standard of care, has this been justified? Have details been given of how the intervention will be allocated? Have details been included of what information participants in the control group will be given?
- Have any plans to withdraw or withhold standard therapies for the purpose of the research been justified?
- What standard of care will be provided for participants who develop diseases or conditions other than those being studied? If it is something less than the best intervention available as part of the national public health system, has this been justified?
- Will research participants be offered payment, gifts or other inducements in return for their participation? Are these appropriate?
- Will there be follow-up and long-term review of the research? If so, have details been given of how this will be carried out?
- Have provisions been made for compensation or treatment in the case of death or injury to research participants?
- Have researchers endeavoured to secure post-trial access for effective interventions for participants in the trial? If not, has the lack of any such arrangements been justified?
- Has consideration been given to the possibility of introducing an intervention shown to be successful to the wider community and maintaining its availability? If it is not thought possible to make the

intervention available to some or all of the population in the country in which the research is to be conducted, can the research be justified?

- Will regular progress reports be made to the research ethics committee? If so, have details been given of how frequently these will occur? Have details been given of any arrangements that have been made for providing proper documentation to the committee?
- Have details been given of how the results of the research will be used? How will the results of the research be disseminated to participants and other interested parties?
- Does the research include provisions for the development of expertise in research within the developing country in which it is to be conducted? If not, is the lack of such provisions justified?

Research conducted with vulnerable populations

- Has the inclusion of individuals in research who cannot consent been justified?
- Is the research question posed important to the health and well-being of this vulnerable population?
- Is the research design appropriate?
- Have safeguards been built into the research design to prevent undue coercion or influence of this group?

170 หน้าว่าง



Fact-finding meetings

172 หน้าว่าง



The Working Party is very grateful to the following individuals¹ for taking the time to meet with members of the Working Party and for providing insights into issues relating to externally-sponsored research in developing countries.

London, UK, 10 April 2000

Dr Gill Samuels, Pfizer (UK)

London, UK, 6 June 2000

Professor Daniel Wikler, Staff Ethicist, World Health Organization (WHO)

Oxford, UK, 17 September 2000

Professor Don Bundy, International School Health Initiative, The World Bank, US
Dr PK Das, Vector Control Research Centre, Pondicherry, India

Dr Nick Day, Centre for Tropical Medicine, University of Oxford, UK

Professor Charles Kihamia, UKUMTA (Tanzania Partnership for Child Development), Dar es Salaam, Tanzania

Dr Martin Meremikwu, Department of Paediatrics, College of Medical Sciences, University of Calabar, Nigeria

Dr Petri Ruutu, Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre, London, UK

Dr Lorenzo Savioli, Strategy Development and Monitoring for Parasitic Diseases and Vector Control and Communicable Diseases Control, Prevention and Eradication, World Health Organization, Geneva, Switzerland

Professor Thor Theander, Institute for Medical Microbiology and Immunology, Panum Institute, University of Copenhagen, Denmark

Dr Bill Watkins

Professor Nick White, Wellcome-Mahidol University Oxford Tropical Medicine Research Programme, Faculty of Tropical Medicine, Mahidol University, Bangkok

London, UK, 6 December 2000

Professor Alan Maynard, University of York

Chennai, India, 21 January 2001

Dr Rani Balasubramanian, Tuberculosis Research Centre (TRC), Chennai

Professor MK Bhan, All India Institute of Medical Sciences, Delhi

Professor George Chandy, Christian Medical College (CMC), Vellore

Professor NK Ganguli, Indian Council of Medical Research (ICMR)

Dr M Gupte, National Institute of Epidemiology

Professor Ravi Jacob Korula, CMC, Vellore

Dr MS Jawahar, TRC, Chennai

Dr L Kameshwaran, Former President, National Academy of Medical Sciences

Dr C Kolapp, TRC, Chennai

Professor R Korula, CMC, Vellore,

Justice Krishnaswamy

Dr Nandini Kumar, ICMR

Dr V Kumaraswami, TRC, Chennai

Dr HN Madhavan, Vision Research Foundation, Chennai

Dr MK Mani, Consultant Nephrologist, Chennai

Dr Rema Mathew, TRC, Chennai

Dr Vasantha Muthuswamy, ICMR

Dr MUR Naidu, The Nizam's Institute of Medical Sciences

1 Institutional affiliations at the time of the meeting are listed

Dr PR Narayanan, TRC, Chennai
Dr S Rajasekaran, TRC, Chennai
Dr Rajeswari Ramachandran, TRC, Chennai
Dr VD Ramanathan, TRC, Chennai
Dr Ravi Rengachari, ICMR
Dr K Sadacharam, TRC, Chennai
Dr MA Salam, The Centre for Health and Population Research (ICDDR-B), Bangladesh
Dr DK Sampath
Professor KR Sethuraman
Professor CH Shashindran, Department of Pharmacology, Pondicherry
Dr H Srinivasan
Dr VK Srinivasan, Indian Institute of Economics
Professor Manorama Thomas, Professor of Anatomy and Human Genetics, Bangalore
Professor Yogesh Tripathy, Kasturba Medical College
Dr KC Umapathi, TRC, Chennai

Boston, US, 22 March 2001

Professor George Annas, Boston University
Professor Barry Bloom, Harvard School of Public Health
Dr Chris Howson, March of Dimes
Professor Robert Levine, Yale University
Professor Ruth Macklin, Albert Einstein College of Medicine

Washington DC, US, 23 March 2001

Dr Finley Austin, Roche
Dr Melody Lin, Office for Human Research Protections (OHRP)
Dr Peter Lurie, Public Citizen
Dr Eric Meslin, National Bioethics Advisory Commission (NBAC)
Mr Paul Ndebele, Johns Hopkins University
Dr Godwin Ndossi, Johns Hopkins University
Dr Duncan Ngare, Johns Hopkins University
Ms Alice Page, NBAC
Ms Maureen Power, National Institute of Allergy and Infectious Diseases (NIAID)
Dr Regina Rabinovitch, Malaria Vaccine Initiative (MVI)
Sara Radcliffe, Pharmaceutical Research and Manufacturers of America (PhRMA)
Dr Gillian Woollet, PhRMA

London, UK, 13 June 2001

Dr Imogen Evans, Medical Research Council (MRC) UK
Dr Richard Lane, The Wellcome Trust

*Method of working and
consultation*

Appendix 5

176 หน้าว่าง



The Working Party met nine times between January 2000 and September 2001. A consultation with the public was held between July 2000 and January 2001 when organisations and individuals with an interest in the topic were invited to comment on the issues raised by research related to healthcare in developing countries. A total of 70 responses were received from over 20 different countries. Respondents included a number of relevant organisations such as sponsors of research, research ethics committees and the pharmaceutical industry, and individuals with expertise in ethics, law, medical research and health policy. Those who responded are listed below and the Working Party is grateful to them all. Some of the main themes to emerge from the consultation responses are set out below.

What kind of research is most beneficial to developing countries?

There was unanimous agreement that research in developing countries should be related directly to the health problems of those countries, and that it should focus on diseases that affect the developing world. Eleven respondents specifically mentioned that it was unacceptable that 90% of the global funds for research related to healthcare was spent on 10% of the population. Some respondents also suggested that a range of research should be carried out, with both short- and long-term benefits, such as basic research into causes and mechanisms of disease, and their diagnosis and treatment. It was also considered important that developing countries were encouraged to define their own research priorities and that partnerships should be developed between those countries hosting and those sponsoring the research. It was also considered very important that the results be made available to the country and community in which the research took place.

In response to the question whether it was morally acceptable for research to be conducted in a developing country when it could also be conducted in a developed country, the majority of respondents considered that it was acceptable, but only if the research was of benefit to those in the developing country. It was generally thought to be unacceptable if research was conducted in a developing country simply because it was cheaper or easier to do so or because of a fear of litigation or a fear of hostile public opinion. However, the view was also expressed that it would be wrong to deny those in developing countries the opportunity to take part in research which offers some direct and indirect benefits. Additionally, it was pointed out that it was sometimes necessary to repeat research in developing countries to determine how effective an intervention might be in the local environment.

One type of harm that might be caused by research related to healthcare in developing countries was the raising of unrealistic expectations of what would be provided to participants once the research was over. Other issues were similar to those faced in developed countries, for example what should happen if participants were harmed as a result of taking part in research and whether compensation would be available for injuries arising from research. A few respondents raised concerns that a lack of infrastructure in developing countries could increase risks associated with research. Others thought that externally-sponsored research might lead to the exploitation of poor and vulnerable populations by more wealthy and powerful ones.

Cultural issues

Consent

The issue of informed consent received the most attention from respondents. It was generally felt to be essential that cultural practices should be recognised in the consent process. Accordingly, the consent process should be flexible and should respect local practices. The majority of respondents thought that although community assent should be sought as well as individual consent, community assent should not be accepted as a substitute for individual consent. Respecting the autonomy of an individual was of

overriding importance. Respondents noted the importance of confidentiality and anonymity for individuals who wished to decline to participate in research, so they did not feel pressured to participate in the research by the community. It was also noted that not all cultural practices were widely supported by those who were subject to them. Some practices were unpopular with people who did not have the power to change them and researchers should be aware of this.

Consent could be obtained either verbally or in writing, but it was noted that signing the consent form was less important than ensuring that participants understood what was involved in the research. Some respondents thought that the benefits of research were often overemphasised, and stressed the importance of making sure that the participants understood the risks involved in the research.

Some respondents noted that it was sometimes difficult to provide adequate information to participants in local languages, particularly when concepts such as placebo and randomisation were unfamiliar. To explain such information required sensitivity and appropriate education.

Alternative therapies

Several respondents noted that many prospective research participants consult traditional healers, or use traditional therapies. It was important to be aware of this behaviour so that research could be set in the appropriate context and any conflicts between the research and traditional therapies could be addressed. Alternative therapies had the potential to influence research results due to real effects or placebo/psychological effects and also posed a challenge in the management of interactions/interference from traditional herbal 'remedies'.

Key ethical issues

Respondents considered that key ethical issues to be addressed in research included autonomy, protection of human rights, respect for persons, beneficence, non-maleficence and justice. It was also considered unacceptable to exploit prospective participants in developing countries for the benefit of those in developed countries. A few respondents suggested that each culture should be able to determine their own ethical framework to apply to research. Others stated that the ethical framework should be the same in developed and developing countries. In particular, it was considered that the balance of benefit and risk to individuals and to the society should depend on the local values of the society.

Inducements to participate in research

Respondents agreed that it was important to show that participants' contribution to research was valued, but differed about how best to do this. One-fifth of respondents suggested that participants should be recompensed for time and loss of earnings. There was a feeling that it was important to de-emphasise financial benefits of participating in research whenever possible and that cash payments should be avoided. Indirect inducements, such as the provision of healthcare, food, education or baby-care items were considered to be acceptable alternatives. The provision of healthcare for children was considered to be particularly appropriate. It was thought that ideally an enduring commitment to the community should be given.

Other respondents took the view that any inducements to participate in research should be sensitive to the context in which the research was conducted. In such circumstances local opinion, including the views of local research ethics committees, should determine if an inducement was acceptable. It was noted that in some communities even offering a meal might amount to a significant inducement to participate in research.

An inducement was considered to be unacceptable if it was so large that a participant would be prepared to assume risks that would otherwise be deemed unacceptable. However, it was pointed out that it would be almost impossible to enforce any rule concerning inducements. One suggestion was that researchers should be liable to a penalty in the event of an unacceptable inducement being offered.

Standards of care

Issues concerning the appropriate standard of care that should be provided during research produced a wide variety of opinions amongst respondents, with no clear division of views between particular types of organisations or between regions of the world.

Many respondents felt that the locally appropriate standard of care should be taken into account. One reason given was that the use of local standards was important for the results of the research to be relevant to the local context. Additionally, providing standards of care comparable to those available in a country sponsoring the research could cause severe imbalances in the level of healthcare available in differing communities within developing countries. In addition, there may be difficulties in sustaining such standards of care beyond the completion of the research. An additional concern was that requiring the standard of care available in a developed country might prevent valuable research from taking place.

However, other respondents took the view that a universal standard of care should be provided. Some respondents thought that research participants should receive the optimal standard of care generally available to those in the community in which the research was to be conducted. Where no treatment was available for a condition, the standard of care available in the sponsoring country should be used.

A compromise that was suggested was that the decision about the standard of care to be used in a specific research project should be made on a case-by-case basis, depending on the local situation. Every effort would need to be made to improve the circumstances under which research took place, and to help improve the local healthcare services for the future.

Current guidance

Overall it was felt that the current guidance on research provided adequate safeguards although the interpretation of some of the guidance was subject to debate. It was noted that it was difficult to enforce the international guidance. Rather than producing new guidance, it was suggested that it would be more useful to increase awareness of the existing guidelines, improve their dissemination and strengthen capacity for their implementation.

There were differing views concerning the need for an additional international regulatory agency to oversee the implementation of guidelines. Some respondents felt this would be helpful, and suggested that such a body could help resolve conflicts of interest. However, others felt that an additional agency would be unlikely to provide substantial help and would not be feasible. It was suggested that a central ethical evaluation committee of an existing body such as the World Health Organization (WHO) should resolve conflicts of interpretation of guidelines.

Respondents from research ethics committees had a number of comments on the guidelines, and in particular the scrutiny of research projects. One suggestion was that externally-sponsored research should receive a form of international review followed by local review in the countries where the research would be conducted. An alternative was to have teams of regional adjudicators licensed by WHO. A third suggestion was for the establishment of partnerships between research ethics committees in the UK and emerging ethical review committees in the developing world to share experience and expertise. Some assessment of proposed research by an organisation that was open to public scrutiny

and conformed to international standards was thought to be important. However, there were differing views about the need for a further international regulatory agency.

Local research ethics committees

Most respondents stressed the need for local research ethics committees, which had an understanding of local customs and traditions. It was considered that these local committees needed to receive adequate training and support to equip them with the necessary knowledge and skills to conduct effective review. It was also important to ensure that different groups of people are adequately represented on such committees. National research ethics committees were thought to have an important role to play and should be encouraged.

It was noted that local research ethics committees were highly susceptible to conflicts of interest, differential relations in terms of power and political exigencies. Particular issues that needed to be addressed were the restraint of influence of prestigious researchers and independence from financial incentives from foreign sponsors.

What happens once research is over

The most common response to the consultation was that interventions shown to be successful should be provided after research to all the participants involved in the study. However, some respondents raised issues about the viability of this approach, noting that, for example, there might not be a mechanism to ensure the correct delivery of a medicine in the longer term. It was considered to be probably inevitable that standards of healthcare would fall once research was complete, but that any phasing out of treatments should be carefully planned in advance. Most importantly, it was suggested that issues related to what happens once the research was over should be addressed in the study design and funding proposals.

Two respondents argued that continuation of a treatment following research was not a requirement in developed countries, and so raised the question whether it should be a requirement in developing countries. Respondents from pharmaceutical companies were concerned that if it was required that a treatment shown to be successful was provided to all of those who needed it within a country, research which might be of benefit to developing countries could not be conducted.

Respondents considered that researchers had an ethical obligation to undertake long-term surveillance of populations who received preventive treatments in research in order to study long-term effects. This was considered to be important for both scientific and ethical reasons, particularly if the preventive treatment being studied might increase the risk of acquiring a disease later in life.

The costs of ongoing provision of treatment

Respondents thought that sponsors of research from the pharmaceutical industry and the public sector, in addition to national governments and other public authorities had some responsibility for the ongoing provision of treatment shown to be effective. Ultimately, it was suggested that the national and local governments held responsibility for the delivery of adequate healthcare to a population. The role of pharmaceutical sponsors was less clear. Some respondents suggested that the pharmaceutical industry should bear all or most of the cost of providing treatment on an ongoing basis, other respondents thought that the industry should be responsible only for providing treatment while the medicine was under licence, while others felt that the industry could not be expected to have a long-term obligation

beyond the period of the research. Genuine partnerships between those involved in sponsoring and conducting research and in providing healthcare were seen to be of importance. Respondents agreed that the provision of a therapy shown to be effective should be discussed prior to the start of any trial.

Is it acceptable to allow research in a community that cannot afford the treatment being tested?

There were differing responses to the question of whether it was acceptable to allow research in a community that could not afford the treatment being tested. Some respondents felt strongly that it was not acceptable under any circumstances. Others felt that the issue of whether or not a treatment could be provided on an ongoing basis was essentially a separate political and economic issue. It was proposed that developing countries should be entitled to decide for themselves whether or not to conduct such research, rather than being excluded on the grounds that they could not afford the treatment. Some diseases only occurred in the developing world and it was thought important not to restrict research into treatments for such diseases on the ground that such treatments could not currently be afforded. It was also suggested that there was no simple answer to the question of whether such research should be conducted, because the cost of a medicine might change, or special prices could be negotiated. Alternative routes for support and supply of a treatment should be considered in the early stages of planning a trial.

Responses to the public consultation

The Working Party wishes to thank the following individuals and their organisations for providing helpful information and insights into the subject of research related to healthcare in developing countries.

Organisations

Association of the British Pharmaceutical Industry (ABPI)

Association of Medical Research Charities (AMRC)

British Union Conference of Seventh-Day Adventists

The Church of England Board for Social Responsibility Science, Medicine and Technology Committee

Glaxo Wellcome plc

HIV/AIDS Vaccine Ethics Group (HAVEG), University of Natal, South Africa

MRC UK

Local and multicentre research ethics committees:

West Berkshire

South Birmingham

Blackburn, Hyndburn & Ribble Valley

Bolton

Bradford

Bromley

Fife Health Board

Glasgow Area Dental Ethics Committee

Gwent

Hartlepool

North Allerton

North Nottinghamshire

Oxford Psychiatric Research Ethics Committee
Plymouth
Salisbury
South Sheffield
South East Staffordshire
Trent multicentre research ethics committee
Ulster University
National Consumer Council
Royal College of Physicians
SmithKline Beecham
Swiss Academy of Medical Sciences Central Ethics Committee
The Wellcome Trust

Individuals

Dr Mohammed Abdus Salam, ICDDR-B, Bangladesh
Professor Adolfo Alvarez
Professor Solomon Benatar, University of Cape Town, South Africa
Dr David E Bratt
Professor Cheryl Cox Macpherson, St. George's University School of Medicine, West Indies
Dr John Dada, Fantsuam Foundation, Nigeria
Professor Bernard Dickens, University of Toronto, Canada
Dr Mike English, Wellcome Trust Research Laboratories, Kenya
Professor EM Essien, University of Port Harcourt, Nigeria
Dr Tamas Fenyvesi, Semmelweis University, Hungary
Professor David Fidler, Indiana University, US
Sitaleki A Finau, University of Auckland, New Zealand
Professor Brian Greenwood, London School of Hygiene and Tropical Medicine, UK
Dr Hemamal Jayawardena, United Nations Population Fund (UNFPA), Sri Lanka
Dr Anatoli Kamali, MRC Research Programme on AIDS in Uganda
Hyo Yoon Kang, European University Institute, Italy
Dr Monica Konrad, University of London, UK
Maureen A Kuyoh, University of Southampton, UK
Angela Kydd
Dr Klaus Lindpaintner, F Hoffman-La Roche
Dr Fernando Lolas, Pan-American Health Organisation (PAHO), Chile
Professor Adetokunbo Lucas, Harvard School of Public Health, US
Dr Dilys Morgan, MRC Research Programme on AIDS in Uganda
Dr Kamran Niaz, United Nations International Drug Control Program (UNDCP), Iran
Dr Pinyupa Plianbangchang, Naresuan University, Thailand
Dr RP Sapru, India
Dr SK Sharif, Provincial Medical Officer/Chief Medical Specialist, Kenya
Dr André Soton, Centre for Regional Development, Benin
Professor Dominique Sprumont, University of Neuchâtel, Switzerland
Professor B Vrhovac, University Hospital Medical School, Zagreb, Croatia
Dr Paul Wangai, Kenya Medical Association, Kenya
Angela Wasunna, The Hastings Center, US
Dr Jimmy Whitworth, MRC Research Programme on AIDS in Uganda

Glossary

184 หน้าว่าง



African Trypanosomiasis

Also known as sleeping sickness, African Trypanosomiasis is a potentially life threatening parasitic disease. The parasites, *Trypanosoma*, are transmitted to humans by tsetse flies. The early stages of the disease are characterised by fever, headaches, pain in the joints and itching. When the parasite crosses the blood-brain barrier and enters the central nervous system, the disease moves into the neurological phase. This is when the characteristic signs and symptoms of the disease appear: confusion, sensory disturbances and poor co-ordination. An additional symptom is disturbance of the sleep cycle, which gives the disease its name. If treatment is not given prior to onset of the neurological phase, neurological damage is irreversible even after treatment.

AIDS (Acquired immune deficiency syndrome)

A disease caused by retroviral infection by the human immunodeficiency virus (HIV-1, HIV-2), that causes immune system failure and debilitation and is often accompanied by infections such as tuberculosis. The disease is transmitted through direct contact with bodily fluids (e.g. blood-blood or via sexual intercourse).

Albendazole (see also Zentel)

An oral medicine used to treat a variety of worm infections.

Antibody

A class of proteins of the immune system which react with and neutralise specific foreign antigens (any substance recognised by the immune system as 'non-self').

Antimycobacterial chemotherapy

Medical treatment for diseases caused by the bacteria *Mycobacterium*, such as tuberculosis and leprosy.

Antiretroviral

A group of medicines used in the treatment of HIV/AIDS.

Artemether

An antimalarial medicine administered intramuscularly.

Ayurveda

Ayurveda means 'the knowledge needed for long life' and is concerned with instruction on personal conduct, including diet, exercise and cleanliness, on keeping the body-soul in equilibrium, and on the diagnosis and treatment of various diseases. Health is maintained and restored through use of herbs,

ointments, enemas, massage and surgery and by attention to balanced levels of food, sleep, exercise and medical ingestion.

Azithromycin (see also *Zithromax*)

An antibiotic medicine commonly used to treat respiratory tract infections, infections of the skin and soft tissues and some sexually transmitted diseases.

Cancer

A disease where cells grow out of control and invade, erode and destroy normal tissue. There are over 200 different types of cancer that can occur anywhere in the body, with different causes and different symptoms.

Carrier state for infectious diseases

When a person harbours disease-causing micro-organisms and can transmit infection to others, though he/she is healthy and without clinical symptoms, he/she is said to be in a carrier state.

Cerebrospinal meningitis

Cerebrospinal meningitis or meningococcal meningitis is a contagious disease caused by the bacteria *meningococcus*. It occurs in both sporadic and epidemic outbreaks, predominantly in children and young adults. The disease is characterised by inflammation of the meninges (three layers of connective tissue that envelop the brain and spinal cord); the symptoms include severe headache, photophobia (light sensitivity) and neck stiffness. The disease can be severe with high mortality rates, or result in permanent neurological disability.

Chloramphenicol

A potent antibiotic which is normally used to treat life threatening infections, particularly those caused by *Haemophilus influenzae* and typhoid fever.

Clinical research and clinical trials (see also *Appendix 2*)

Medical research studies designed to answer scientific questions and to find better ways to prevent, detect, or treat disease. A large number of clinical trials are confined to testing the safety and efficacy of new medicines. There are four separate phases of such trials:

Phase I trials

Phase I studies will be the first time human subjects are exposed to the potential novel medicine. The objectives behind the study will be to investigate pharmacodynamics, dose-response, and in the case of vaccines, immune response, and to determine the maximum dose that can be tolerated by participants. In the case of most new medicines these studies will be undertaken in a small number of healthy

volunteers. It is not expected that evidence of efficacy of the medicine will be provided by Phase I studies.

Phase II trials

Using the information regarding the safe dosage range obtained from the Phase I studies, the compound will be administered to patients suffering from the target disease and now significant numbers of individuals will be recruited into the trial. Almost always these trials will be conducted in a number of clinical centres. The objective of the Phase II studies will be to seek evidence of the efficacy of the medicine against the specific disease. More information about the safety of the medication will emerge from these studies as larger numbers of individuals are exposed to it. In Phase II trials the patient will often be randomly assigned to the novel treatment group or to a group receiving a placebo (a compound possessing no therapeutic effect) or, more usually, a conventional and established treatment.

Phase III trials

Where a compound has shown evidence of efficacy without significant side effects it will enter Phase III trials in which many hundreds, or sometimes a few thousand patients will be enrolled. These trials will generally seek not only to confirm the clinical efficacy of the novel compound, but also to establish its efficacy in comparison with existing treatments. These studies will often be multicentre and sometimes undertaken on an international basis. Again, careful attention is paid to possible side effects as larger numbers of patients are exposed to the intervention. The end-points for Phase III studies include the demonstration of a statistically significant improvement in the efficacy of the novel medicine over the established therapies, if any such exist.

Phase IV trials

Once a new medicine reaches the market it will be subjected to post-marketing surveillance in order to identify side-effects and other adverse effects which would only become evident as much larger numbers of individuals are treated with. In addition, formal clinical trials continue in order to develop a greater understanding of the compound and its effects in a wider clinical environment, but also to extend its use for other indications or for different patient groups, such as children or the elderly. Special study designs may be used according to the objectives of the study to evaluate safety or efficacy. These may include study of temporal trends, case-control studies, or the phased introduction of an intervention in different areas. Phase IV studies may also be designed to measure the impact of the intervention on the epidemiological pattern or transmission of an infectious disease.

Communicable diseases (see also *non-communicable diseases*)

Communicable or infectious diseases are caused by living organisms, mainly micro-organisms (e.g. viruses, bacteria and fungi and groups intermediate between viruses and bacteria e.g. chlamydiae). The source of disease can be another human, animal or insect. Transmission occurs via several routes (e.g. physical contact, food and drink) and organisms typically enter the body by inhalation or direct contact.

Compulsory licensing

A legal intervention to restrict the monopoly rights of existing patent holders and make generic medicines or diagnostics (e.g. clinical tests) more available.

Conjugate

Paired together, such as in pneumococcal conjugate vaccines for pneumonia and meningitis.

Control

A control group in clinical research and clinical trials (see *clinical research and clinical trials*) contains participants who are not given the intervention which is being tested in the research and compared with a group who are given the intervention. In clinical trials, the intervention would normally be a novel treatment, such as a medicine or vaccine but interventions may also be social and behavioural in nature, for example, safe sex campaigns.

Diarrhoeal disease

Any group of diseases causing diarrhoea as the main symptom, i.e. an abnormal increase in the frequency and/or liquidity of the stools, which in developing countries (particularly in children) may be fatal.

Eflornithine

An antiprotozoal medicine used to treat African trypanosomiasis (sleeping sickness) (see *African trypanosomiasis*).

Elephantiasis

Gross swelling, usually affecting the legs and genitalia caused by chronic lymphatic obstruction by filarial worms (see *Lymphatic filariasis*).

Epidemic

A temporary increase in the prevalence of a disease within a specific community or region. The rise in prevalence may last a few weeks or years.

Epidemiological research (see Appendix 2)

Research concerned with describing and explaining the occurrence of disease in populations.

Generic medicines

Generic medicines are chemically the same as brand name medicines. They have the same characteristics (e.g. intended use, dosage, route of administration, safety, and quality) but are typically much lower in price than their branded counterparts.

GNP (gross national product) per capita

GNP per capita reflects the average income of a country's citizens. It is calculated by dividing the final output of a country's goods and services in a year by the country's population.

GOBI-FFF

Growth monitoring, oral rehydration, breastfeeding, immunisation, food supplementation, family planning, and female education.

A programme of simple and inexpensive methods aimed at reducing child mortality.

Goitre

An enlargement of the thyroid gland, caused primarily by stimulation of the gland by the thyroid-stimulating hormone (TSH). This can be produced by iodine deficiency and excess or by certain foods and medications.

Hepatitis B

A virus transmitted through body fluids by poor surgical sterilisation procedures, close contact, blood contamination, infection at birth, needle sharing or sexual contact. It causes an acute illness, which may develop into chronic hepatitis. Symptoms include tiredness, sickness, fever, loss of appetite, stomach pains, and diarrhoea. Symptoms may also include dark yellow urine, and yellowish eyes and skin (also called jaundice).

Hepatitis E

A virus transmitted by faecal or oral routes, causing an acute resolving illness marked by inflammation of the liver and jaundice. It may be fatal during pregnancy.

Hib disease

Hib disease is a group of diseases caused by the *Haemophilus influenzae* type b bacteria e.g. pneumonia and bacterial meningitis.

Hib polysaccharide – protein conjugate vaccine

A vaccine for *Haemophilus influenzae* type B containing a “weak” polysaccharide (complex naturally occurring carbohydrates e.g. starch) linked to a protein.

Hippocratic oath

The oath attributed to the Greek physician, Hippocrates who is known as the father of medicine, which doctors have traditionally taken upon graduation, on the duties, obligations, and ethics of practising medicine.

Hydroxyurea

An anti-cancer medicine, used mainly in the treatment of chronic myeloid leukaemia (a cancer of the myeloid leucocytes, a type of white blood cell). Used in conjunction with anti-HIV medicines, it may also improve their efficacy in treating HIV infection.

Hypertension (anti-hypertensives)

Persistently high arterial blood pressure, which may have no known cause or be associated with other diseases. Hypertension is a risk factor for the development of diseases such as heart disease and stroke.

Infectious diseases

See *communicable diseases*.

Ivermectin

One of a class of medicines used to treat infestation with several species of nematode worms transmitted by biting insects. It is used as the medicine of choice for the treatment of onchocerciasis.

Leishmaniasis

A parasitic disease caused by the protozoa *Leishmania*, transmitted by the bite of some species of sand fly. Various forms of the disease are known, depending on the species of parasite. One form is visceral leishmaniasis, characterised by fever, enlargement of the spleen and liver, and anaemia. Symptoms typically develop over months, but can take years following infection. Most cases of visceral leishmaniasis occur in Bangladesh, Brazil, India, Nepal, and Sudan.

Leprosy

A chronic infectious disease caused by the bacteria *Mycobacterium leprae*. The disease mainly affects the skin and the peripheral nerves. The precise mode of transmission remains uncertain, but is from person to person, and close and prolonged contact is thought to be necessary.

Low dose spiral computed tomography

Computed tomography (CT) is a method by which an X-ray image of a cross-section of the body or head is reconstructed electronically and displayed. Low dose spiral computed tomography is a type of CT useful in the early detection of cancers, especially peripheral lung cancer.

Lumbar puncture

An invasive diagnostic test in which a needle is injected into the lower part of the spine canal to extract cerebrospinal fluid (CSF) for examination. This is used to diagnose, or rule out, certain diseases such as meningitis.

Lymphatic filariasis

Lymphatic filariasis is a parasitic disease caused by a worm transmitted by certain kinds of mosquitoes. Worms accumulate in the lymphatic system and may cause gross swelling of the legs (elephantiasis), and scrotum (hydrocoeles) and other body areas.

Magnetic resonance imaging (MRI)

A technique used to image internal structures of the body, particularly the soft tissue.

Malaria

Malaria is a tropical, parasitic disease transmitted by Anopheline mosquitoes. Symptoms include fever, shivering, pain in the joints, headache, repeated vomiting, generalised convulsions and coma. Left untreated, the disease may result in death.

Malarone

An anti-malarial medicine.

Measles

An acute infectious viral disease which, in Western urban communities, prior to the introduction of immunisation programmes, largely affected children. Immunisation programmes resulted in the incidence shifting to the unimmunised young adult population. The disease is characterised by symptoms such as a rash usually beginning in the mouth, high temperature, headache, and photophobia (light sensitivity). The disease is normally self-limiting but complications can occur through secondary infection (e.g. pneumonia) and the disease still has high mortality rates in the developing world.

Mefloquine

An anti-malarial medicine, particularly used in areas of the world where there is a high risk of chloroquine-resistant falciparum malaria.

Meningococcal meningitis

See *cerebrospinal meningitis*

Methadone

A medicine, belonging to the morphine family, used for pain relief, administered either orally or by subcutaneous or intramuscular injection.

Miltefosine

An anti-cancer medicine administered by mouth that is also being tested as an oral treatment for Leishmaniasis.

Morbidity

Levels of sickness and ill health.

Natural history of a disease

The description and classification of a disease, often with emphasis on the course of the disease without the influence of interventions.

Neglected diseases

Diseases which may be very common but because of market systems and lack of a population able to afford treatments, are not subject to wide-scale research and development.

Nevirapine (see also *Viramune*)

One of a class of medicines normally used in the treatment of progressive or advanced HIV infection, in combination with at least two other antiretroviral medicines. Recent studies have demonstrated the efficacy of the medicine in reducing perinatal transmission of HIV, where a single dose of the medicine is administered to the mother during labour and a single dose is given to the child within 72 hours of birth.

Non-communicable diseases (see also *communicable diseases*)

Diseases caused by factors other than living organisms, such as lifestyle, diet, genes or a combination of factors. Examples of non-communicable diseases include mental disorders, heart disease, and cancer.

Non-infectious diseases

See *non-communicable diseases*.

Onchocerciasis ('River Blindness')

Onchocerciasis is a parasitic disease transmitted by simulium flies, which breed in fast-flowing rivers and streams. The parasites migrate about the body, including to the eyes where they may cause blindness.

Pathogen

Any disease-causing agent, but particularly disease-producing micro-organisms.

Pathogenesis

The mode of production or development of a disease.

Perinatal transmission

Transmission of an infection-causing agent, such as HIV, from mother to child in the period either shortly before or after birth.

Pharmacogenetics

The study of how genetic differences influence the variability in patients' responses to medicines.

Placebo

A treatment known to be without effect, usually used as a control to be compared against a potentially effective substance or method which is being subjected to clinical trial.

Pneumonia

Inflammation of the lungs due to infection with micro-organisms.

Poliomyelitis ('polio')

A disorder caused by infection with the *poliovirus* that affects the whole body, including muscles and nerves. Severe cases may cause permanent paralysis or death. Transmission of the virus occurs by direct person-to-person contact, by contact with infected secretions from the nose or mouth, or by contact with infected faeces. An oral vaccine is available as a preventive measure. Any treatment is based on the presence and severity of symptoms, but may involve administration of antibiotics (e.g. for urinary tract infections) or analgesics (for pain relief), or moist heat to reduce muscle pain and spasm. In severe cases, life-saving measures, particularly to assist with breathing may be required. Interventions (e.g. physical therapy) to maximise recovery of muscle strength and function may also ultimately be needed.

Praziquantel

A medicine used in the treatment of blood fluke worm infections, which cause the disease schistosomiasis (also known as bilharziasis) (see *Schistosomiasis*).

Prophylactic

Preventive measure, including medication.

Prophylactic chemotherapy

Preventative medicine treatment for diseases such as tuberculosis and certain types of cancer (e.g. Non-Hodgkin's lymphoma).

Protease inhibitors

A class of medicines used in the treatment of HIV infection.

Quorate

A quorum is the minimum number of members that must be present to constitute a valid meeting, where decisions can be taken concerning submissions put forward for ethical review. A meeting is quorate when a quorum is present.

Randomised controlled trials

An experiment in which investigators randomly allocate eligible participants into control and intervention groups to receive one or more interventions that are being tested. The results are assessed by comparing outcomes of the two groups. (See also *Control*)

Rectal artesunate

An anti-malarial medicine administered as a suppository.

Rhinitis

Inflammation of the mucous membranes in the nose.

Rotavirus oral vaccines

Vaccines for immunisation against rotavirus, the commonest cause of severe diarrhoea among children worldwide.

Schistosomiasis

Also known as bilharziasis. Schistosomiasis is a disease caused by infestation with parasitic trematode worms. The disease is endemic in over 70 developing countries. The parasite enters the body through contact with infested surface water, mainly among people engaged in agriculture and fishing. Symptoms may initially include itchy skin and a rash, followed by fever, chills, cough, and muscle aches. It is common for people to present with no symptoms at the early phase of infection. In rare cases, seizures, paralysis, or spinal cord inflammation may occur. Repeat infection is possible which can result in damage to the liver, intestines, lungs, and urinary tract. Control of the disease may be directed at medicine treatment, control of the host (snails), improvements in personal hygiene or sanitation or a combination of all three.

Shaman

A shaman is someone who is believed to mediate between the spirit world and humanity, and is able to enter into a trance or similar state and then diagnose and prescribe or effect cures for disease. The term was originally coined by scholars who were studying societies in Siberia and central Asia, and was later extended to similar religious complexes found elsewhere in the world.

Sickle cell disease

A genetic disorder caused by an abnormality of the haemoglobin molecule, which carries oxygen in the blood. The disease is characterised by chronic haemolytic anaemia (a deficiency in the number of red blood cells caused by reduced cell survival time and the release of haemoglobin, which results in an insufficient supply of oxygen to tissues and organs), sickle-shaped deformity of the red blood cells, and complications relating to aggregations of sickle cells in blood vessels (e.g. infarction or death of tissue and bodily organs due to inadequate blood supply). The disease is only fully expressed in the homozygous state (i.e. where the gene has been inherited from both parents). The heterozygous state (when an abnormal gene has been inherited from one parent and a normal gene from the other) is thought to confer some protection against falciparum malaria in endemic areas.

Sleeping sickness

See *African trypanosomiasis*.

Stroke

A sudden impairment of brain function due to bleeding (haemorrhage) from or obstruction to one or more cerebral blood vessels.

Tetanus

Tetanus or 'lockjaw' is an acute, infectious disease caused by the anaerobic, spore-forming bacillus *Clostridium tetani*. The agent most often enters the body through contaminated puncture wounds (caused by, for example, rusty nails) or via other means such as burns and ulcers. The disease can be fatal as a result of respiratory difficulties or exhaustion.

Tiered pricing

Differential pricing of medicines based on consideration of a country's economic status.

Titre

The quantity of a substance required to produce a reaction with, or correspond to, a given quantity of another substance.

Trachoma

Trachoma is caused by the bacteria *Chlamydia trachomatis*, which is highly contagious. Repeated infections cause eyelashes to turn inwards, scarring the eye and leading to blindness in adult life.

Tuberculosis

A serious infectious disease caused by a species of *Mycobacterium*. The disease can involve almost any organ or tissue of the body, but the lungs are most commonly affected. Symptoms include a persistent

cough, fever, weight loss, constant tiredness, and loss of appetite. The disease is highly contagious and is spread through the air.

Vector

An animal carrier of the agent of a communicable disease.

Viramune

The brand name for nevirapine (see *Nevirapine*).

Yellow fever

An acute viral infection caused by a group B arbovirus and transmitted by mosquitoes of the *Aedes* and *Haemagogus* type. The disease varies in severity from a mild influenza-like episode to a dangerous and sometimes fatal illness marked by jaundice due to liver necrosis, haemorrhaging (bleeding), and renal failure.

Yunani

A branch of traditional medicine, common to Muslim areas on the Indo-Pakistan subcontinent. This is the medicine of the ancient Greeks, translated into Arabic and Persian and then slowly modified by its practitioners, the Hakim. The system is based around the four humors: yellow bile, black bile, phlegm, and blood, which combine with four primary qualities of heat, cold, moisture, and dryness. Illness is thought to result from the disequilibrium of the humors and qualities.

Zentel

Brand name for the medicine Albendazole (see *Albendazole*).

Zidovudine

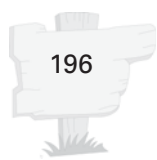
An antiviral medicine now used mainly in developed countries in the triple medicine combination for the treatment of HIV/AIDS.

Zithromax

Brand name for the medicine Azithromycin (see *Azithromycin*).

Glossary of Acronyms

AIDS	Acquired immune deficiency syndrome
AMA	American Medical Association
AMRC	Association of Medical Research Charities (UK)
AMVTN	The African Malaria Vaccine Testing Network
AZT	Azidothymidine (more recently called zidovudine)



CDC	Centers for Disease Control and Prevention (US)
CHRD	Commission on Health Research for Development (Switzerland)
CIOMS	Council for International Organizations of Medical Sciences
COHRED	Commission on Health Research for Development
CONEP	Central Committee of Ethics in Clinical Research (Brazil)
CPMP	Committee for Proprietary Medicinal Products (Europe)
CSM	Cerebro-spinal meningitis
DALYs	Disability adjusted life years
DfID	Department for International Development (UK)
DHHS	Department of Health and Human Services (US)
DSMC	Data and safety monitoring committee
EC	European Commission
EFGCP	European Forum for Good Clinical Practice
ENHR	Essential national health research
FDA	Food and Medicine Administration (US)
FECCIS	Forum for Ethics Committees in the Confederation of Independent States
FERCAP	Forum for Ethical Review Committees in the Asian and Western Pacific Region
FERCIT	Forum of Ethical Review Committees in Thailand
FLACEIS	Foro Latino Americano de Comités de Ética en Investigacion en Salud
GAVI	Global Alliance for Vaccines and Immunization
GNP	Gross national product
GOBI-FFF	Growth monitoring, oral rehydration, breastfeeding, immunization, food supplementation, family planning, and female education
GPPP	Global public private partnership
GSK	GlaxoSmithKline
HAVEG	HIV/AIDS Vaccine Ethics Group (University of Natal, South Africa)
Hib	<i>Haemophilus influenzae</i> type b
HIV	Human immunodeficiency virus
HIV-NAT	The HIV Netherlands Australia Thailand Research Collaboration
IAVI	International AIDS Vaccine Initiative
ICH	International Conference on Harmonisation
ICDDR-B	International Centre for Diarrhoeal Diseases Research, Bangladesh
ICMR	Indian Council of Medical Research
IRB	Institutional review board
MHC	Maori Health Committee (of the Health Research Council of New Zealand)
MMV	Medicines for Malaria Venture
MRC	Medical Research Council (UK)
MRI	Magnetic resonance imaging
MVI	Malaria Vaccine Initiative
NBAC	National Bioethics Advisory Commission (US)
NGO	Non-governmental organisation
NHMRC	National Health and Medical Research Council (Australia)
NIH	National Institutes of Health (US)
PABIN	Pan African Bioethics Initiative
PAHO	Pan American Health Organization
PhRMA	Pharmaceutical and Research Manufacturers of America
PRISM	Unit for Policy Research in Science and Medicine (UK)
SIDCER	Strategic Initiative for Developing Capacity in Ethical Review
STD	Sexually transmitted disease
TB	Tuberculosis

TDR	UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WMA	World Medical Association
WTO	World Trade Organization

Index

200 หน้าว่าง



- Aboriginal and Torres Strait Islanders, research guidance 63, 76, 150
- adverse effects
 - giving information on 75
 - post-trial responsibilities 116–18, 153–4
 - see also risks, research
- Afghanistan, infant mortality 16, 17
- Africa
 - consent 44–5
 - ethical review 109
 - health indicators 15, 16, 17, 19
 - schistosomiasis 92
 - traditional medicine 40
 - see also specific countries
- African Malaria Vaccine Testing Network (AMVTN) 109
- after the trial see completion, study
- AIDS see HIV infection/AIDS
- albendazole 30, 31
- alternative medical systems 39, 178
- altruistic beliefs 45–6
- American Medical Association (AMA) 60
- Angell, Marcia 8, 89
- annual reports, research progress 107
- Anopheles stephensi* 25
- antimalarial drugs 33, 121–2
- antiretroviral drugs
 - costs 33–4, 122
 - pregnant women 8, 93, 117, 122, 124
- Argentina 104
- artemisinins 33
- Asia
 - disability-adjusted life expectancy 16
 - ethical review 109
- audio tapes 74, 82
- Australia, national guidance 63, 76, 150, 151
- autonomy, individual 43, 57
- Ayurvedic system 39
- azithromycin 26, 31

- basic research 25, 163
- bed-nets, insecticide-impregnated 31, 118, 119, 123
- behavioural research 25, 163
- belief systems, local 40–2, 74–5
- Belmont Report (1979) 64, 150, 159
- benevolence 57
- benefits (of research) 125, 177
 - duty to provide 53, 90–1
 - indirect 29, 31, 131
 - to participants 78, 79, 91, 115, 131
- Bill and Melinda Gates Foundation 27, 29
- blood samples 41, 71
- Brazil
 - consent 76
 - ethical review 104
 - national guidance 151, 152, 153, 156–7
- Burkina Faso 40
- Burkitt's lymphoma 29, 31

- Canada, national guidance 151
- cancer
 - diagnosis 73
 - liver 93
 - screening 25, 89
- capacity (to give consent) 76–7
- Caribbean 19, 109
- Centers for Disease Control (CDC) 27
- cerebro-spinal meningitis 8
- cervical cancer screening 25
- charities 27, 29
- child mortality rates 16–17, 18
 - interventions reducing 31, 122–3
- children
 - immunisation 17
 - participation in research 44, 71, 76–7
- Chile, motivation of participants 45–6
- China
 - community consultation 44
 - national guidance 151
 - traditional medicine 39
- chloroquine 33
- chronic disease 103
- CIOMS/WHO guidelines 58, 59, 61–2, 157
 - on consent 72, 78, 79, 80
 - enforcement 65
 - on ethical review 101, 154
 - on post-trial responsibilities 114, 115, 116
 - on standards of care 88
- clinical research 25, 163
- clinical trials 28–9, 163
 - for benefit of developed countries 125
 - control groups see control groups
 - implementing results 113, 120–1
 - international guidance 61, 62
 - national guidance 64
 - standards of care 61, 62, 89–92
 - supply of drugs for 34
- co-artemether 33
- collaborative research projects 126
- Colombia, consent 45
- colonialism, legacy of 46
- Commission on Health Research for Development 21–2, 26, 30, 125–6
- communicable diseases 17, 19
 - need for new interventions 32
- communication infrastructure 21
- community
 - assent/involvement 43–4, 71, 76–7, 135
 - consultation 43, 44, 74, 75–6, 133
 - implementing research results 113, 116, 119, 121–2, 142–3
 - respect for 43
- community leaders
 - assent/involvement 76–7, 135
 - trust in/respect for 43
- compensation
 - for adverse effects 116–17, 153–4
 - see also fees; payments
- competence (to give consent) 71
- complementary therapies 39
- completion, study 9–10, 113–26, 141–3
 - consultation views 180
 - ethical review of arrangements 103
 - guidance 61, 62, 114–15, 120, 121–2, 156
 - recommendations 116, 120, 121, 125, 126, 141, 142–3
- condoms 31
- confidentiality 7, 73
- conflicts of interest 105, 180
- consent 6–7, 71–83, 135–7
 - community involvement 76–7, 135
 - confidentiality issues 7, 73
 - cultural issues 43–6, 52, 72–3, 80, 177–8
 - essential elements 65
 - ethical review of procedures 81–2, 83, 103
 - forms 7, 80–3, 136–7
 - genuineness 71–3, 77, 135
 - information for see information
 - recommendations 77, 80, 83, 136, 137
 - recording 80–3, 136–7
 - refusal 77–8, 136
 - verbal 82, 83, 137
 - voluntariness 71, 75–80, 135–6
- contraceptives 31
- control groups
 - placebo therapy 8, 61, 62
 - post-trial care 118, 119–20, 142
 - standards of care 7, 61, 89–97, 138–9
- cost-benefit analysis 122
- costs
 - drug development 32–3
 - fall over time 9, 34, 123–4
 - interventions 9, 31, 33–4, 123–4, 180–1
 - research ethics committees 106–7, 140
- Cote d'Ivoire 93
- Council on Health Research for Development (COHRED) 26
- Council for International Organisations of Medical Sciences
 - guidelines see CIOMS/WHO guidelines

- cultural assistants 42
cultural context 39–46, 133
 consent 43–6, 52, 72–3, 80, 177–8
cultural differences, sensitivity to 51–2, 134
 conflicts 77, 135
 in practice 53, 73, 135
Czech Republic 104
- Data and Safety Monitoring Committee (DSMC) 116
death, concepts of 40–2
decision making, about research 43–4, 71, 75–7
Declaration of Helsinki *see* Helsinki Declaration
Denmark, national guidance 63
Department for International Development (DFID) (UK)
 25, 27, 28
designs, research 93, 138, 163
diagnosis, information about 73, 135
diarrhoeal diseases 34
disability-adjusted life expectancy 16
disability-adjusted life years (DALYs) 17, 19
disease, concepts 40–2
doctors
 ethical guidance 65
 numbers 20, 21
 patient relationships 42–3, 73
 trust in/respect for 41, 78
drugs *see* medicines
- economic context 15–35, 132
education 21
 see also training
elders, community *see* community leaders
elephantiasis 31
empire, legacy of 46
epidemiological research 25, 62, 163
equality 90, 137–8
equipment, research 126, 143
essential national health research (ENHR) strategies 26–7
Ethical Considerations in HIV Preventive Vaccine Research
 (UNAIDS) 58, 59, 62, 157
 on ethical review 101
 on post-trial responsibilities 114
 on standards of care 88, 96, 139
ethical framework 49–53
ethical principles 6, 49–53, 131, 133–4
 alternative terminology 57
 key 178
 translation into practice 53
ethical review 9, 101–9, 140–1
 consent procedures 81–2, 83, 103
 developing capacity for 108–9, 132
 guidance 101, 105, 154–6
 issues to be considered 167–9
 levels of assessment 102, 140
 post-trial aspects 142–3
 recommendations 102, 106–7, 108–9, 140–1
 requirements for effective 103–6
 in sponsor and host countries 107–8, 140–1
 versus scientific review 102
 see also ethics committees, research
ethics committees, research 9, 53, 101–9, 140–1
 ad hoc decisions 104–5
 conflicts of interest 105, 180
 consultation views 180
 countries lacking 104, 105
 disagreement between 107, 141
 financial support 106–7, 140
 frequency of meetings 106
 independence 106–7, 140
 membership 105
 requirements for effective 103–6, 140
 training of members 105, 108–9, 141
Europe
 ethical review 104, 109
 research funding 27, 28
 research guidance 58, 64, 157
evidence base 22
expenditure, research
 by external sponsors 22–3, 24
 premature mortality and 21–2
expertise, developing local
 in healthcare 116, 141
 for research 22, 125–6, 131–2, 143
 see also training
exploitation, avoidance of 52–3, 57, 131, 134
 inducements and 79
 post-trial access to interventions and 113, 118
 standards of care and 90, 137
externally sponsored research
 ethical review 102, 107–8, 140–1
 guidance 57, 64
 recommendations 131
 relevance to local priorities 27, 28–30, 131
 scope 22–4
- fact-finding meetings 173–4
faeces, samples of 41
fairness *see* justice
family
 decisions about research 43–4, 71
 respect for 43
 senior members, assent by 76–7, 137
Fansidar 33
feasibility studies 25
fees
 to research ethics committees 106, 140
 see also payments
filariasis, lymphatic 31
financial support *see* funding
Finland, national guidance 151
Fogarty International Center 108
Food and Drug Administration (FDA) 22–3
fora, regional, for developing capacity for ethical review 108, 109
France, national guidance 150
funding
 agencies, research *see* sponsors, research
 research ethics committees 106–7, 140
- The Gambia
 consent 82–3
 Haemophilus influenzae type b vaccine 34, 119, 124
 hepatitis B vaccination 9, 124
 HIV vaccine 28
 insecticide-treated bed-nets 123
genetic research 34–5, 75
Geneva Declaration 147
Ghana, traditional medicine 40
GlaxoSmithKline (GSK) 29, 30
Global Alliance for Vaccines and Immunization (GAVI) 27, 30
global public-private partnerships (GPPPs) 23, 27, 32
GOBI-FFF 122–3
goitre 123
good clinical practice guidelines 62
governmental bodies, funding research 27, 28
governments
 decisions on levels of care 138
 funding research ethics committees 106
 implementing trial results 122, 123–5, 142–3, 180–1
gross national product (GNP)
 per capita, life expectancy and 17–20
 proportion spent on health 20–1
guidance 57–66, 134–5, 147–59
 available on internet 157–9
 completion of study 61, 62, 114–15, 120, 121–2, 156
 consent 71, 78
 consultation views 179–80
 contradictory 65, 66
 enforcement 64–5, 179
 ethical review 101, 105, 154–6
 historical context 57–8
 implementation 59
 information provision 60–1, 72
 international 58, 59–62
 national *see* national guidance
 recommendations 66, 134–5
 standards of care 57, 61, 87–8, 96, 152–4

- guidance (*continued*)
 training in interpreting/applying 65–6, 134–5
 see also *specific guidelines*
- Guidance on Good Clinical Practice (ICH) 62, 88, 101, 154, 157
- Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products (WHO) 62, 88, 101, 114, 157
- Guinea Bissau 104, 117–18
- Haemophilus influenzae* type b (Hib) vaccine 34, 119, 124
- halofantrine 33
- harm
 prevention of avoidable 91–2, 117
 see also *risks, research*
- healers, traditional see *traditional healers*
- health
 determinants 5
 inequalities 15–17, 131, 132
- healthcare
 continuation of improvements 115–16
 development of local expertise 116, 141
 implementing changes 122–3
 as inducement to participate 78, 79, 136
 research needs 5–6
 resources, variations between countries 17–21
 standards see *standards of care*
 see also *interventions; treatment*
- healthcare workers
 information provision 74, 78
 trust in/respect for 42
- health expenditure
 per capita 20
 as proportion of GNP 20–1
- health systems
 research 26, 163
 standards of care available 94
- Helsinki Declaration 58, 59–61, 147–50, 157
 on consent 72, 78
 enforcement 65
 on ethical review 101
 on post-trial responsibilities 114, 115, 120
 revisions 60
 on standards of care 61, 87, 88
- hepatitis B vaccine 9, 34, 124
- hepatitis E 30
- HIV
 counselling and testing 9, 25
 drugs see *antiretroviral drugs*
 research sponsors 27, 28, 30
 vaccines 25, 27, 28, 96, 139
- HIV infection/AIDS 5, 17
 confidentiality issues 7, 73
 donation of condoms 31
 low-cost treatment 8, 125
 perinatal transmission trials (1997) 6, 7, 8, 57, 93–4
 prevention of perinatal transmission 93, 117, 122, 124
 standards of care 95
 STDs and 95, 97
 TB prophylaxis 95
 traditional healthcare 40
- human immunodeficiency virus see *HIV*
- ICH see *International Conference on Harmonisation*
- illiterate populations, recording consent 17, 81, 82, 136–7
- illness
 concepts 40–2
 in preventive studies 96
 unrelated, standard of care 97, 139
- immune cells 75
- immunisation, childhood 17
- implementation, research results 9–10, 113, 119–25, 142–3
- India
 ethical review 104
 infant mortality rates 16–17
 national guidance 117, 151, 152, 155, 156
 inducements 71, 78–80, 103, 136, 178–9
 see also *payments*
 infant mortality rates 16–17
- infectious diseases see *communicable diseases*
- information 43, 71–5, 133, 135
 on complex and novel concepts 74–5
 ethical review of procedures 103
 guidance 60–1, 72
 on post-trial interventions 120
 on research results 123
 sheets 81, 82, 83, 136
 understandable 74
- infrastructure development 21
- injections 41
- insecticide-impregnated bed-nets 31, 118, 119, 123
- international agencies 27–8
 post-trial responsibilities 123–5, 142–3
- International AIDS Vaccine Initiative (IAVI) 27, 32
- International Code of Medical Ethics 147
- International Conference on Harmonisation (ICH) 58, 59, 65, 157
 on ethical review 101, 154
 on standards of care 88
- International Ethical Guidelines for Biomedical Research Involving Human Subjects see *CIOMS/WHO guidelines*
- International Guidelines for Ethical Review of Epidemiological Studies see *CIOMS/WHO guidelines*
- International Trachoma Initiative (ITI) 26
- interpreters 42, 78
- interventions
 adverse effects see *adverse effects*
 affordability 9, 31, 33–4, 113, 123–4, 180–1
 developing new 30–4
 donated/subsidised 31, 33–4
 evidence base 22
 post-trial availability 103, 113–16, 118–25, 141, 142–3
 see also *treatment*
- intervention studies 163
- investigators see *researchers*
- iodination of salt 123
- isolated areas, standards of care 96
- ivermectin 31, 124
- Ivory Coast 7
- Jamaica, ENHR strategy 26
- Japan 16, 17
- justice 57, 90, 131, 137
- The Lancet 8, 9
- lancets 91
- language 63, 72
- Laos 104
- Latin America
 consent 45
 ethical review 104, 109
 health indicators 16, 19
 US-sponsored research 23, 24
- lay members, research ethics committees 105
- leaders, community see *community leaders*
- legal liability 81
- leprosy 7
- life expectancy
 disability-adjusted 16
 GNP per capita and 17–20
 trends 17, 21
 variations between countries 15–17
- liver cancer 93
- lung cancer screening 89
- malaria 25
 affordable interventions 31
 expenditure on research 23
 medications 33, 121–2
 post-trial care/surveillance 118, 119
 public-private partnerships 23, 27
 research sponsors 27, 28, 30
 traditional healthcare 40
 vaccines 109, 117
- Malaria Vaccine Initiative (MVI) 27, 30
- Malarene 27, 31, 33
- Malawi, blood samples 41

- Maori communities 63, 76
 measles vaccines 117–18
 Medical Research Council (MRC) (UK)
 guidance 71, 151, 152, 156, 158
 research funding 25, 27, 28, 117, 123
 Medical Research Council of South Africa 126, 151, 158
 medicines
 development of new 32–3, 34–5
 donated/subsidised 31, 33–4, 124
 generic versions 33–4
 see also vaccines; *specific drugs*
 Medicines for Malaria Venture (MMV) 23, 27
 meetings
 fact-finding 173–4
 public 43, 74, 123
 mefloquine 33, 121
 men, decision making by 43–4, 45
 meningitis
 cerebro-spinal 8
 meningococcal 96
 Michigan State University 25
 misfortune, concepts of 40–2
 molecular medicine 34–5
 monitoring
 post-trial 116–18, 142–3
 by research ethics committees 107, 142
 moral relativism 51–2, 134
 mortality, research expenditure and 21–2
 mosquitoes, malaria 25
 mothers-in-law 44
 motivation, research participants 45–6, 78, 136
 multi-disciplinary research 66
 Myanmar 104
- National Bioethics Advisory Committee (NBAC) (US) 46,
 64, 158
 on consent 82
 on post-trial access to interventions 103, 115, 120, 121,
 156
 on standards of care 152, 154
 national guidance 62–4, 150–1
 available on internet 158–9
 development 65, 66, 135
 on specific topics 152–7
 National Institutes of Health (NIH) (US) 63, 108, 123
 national priorities for research, setting 24–7, 28, 132–3
 national standards of care 94–5, 138–9
 natural history of disease 25
 neglected diseases 32–3
 Nepal, national guidance 151
 Netherlands, national guidance 151
 nevirapine 124
 New England Journal of Medicine 8, 89
 New Zealand, national guidance 63, 76, 151
 Nigeria 96, 122–3
 non-therapeutic research 61, 71
 Nuremberg Code 57–8
 nurses, numbers of 20, 21
 nutrition 21
- onchocerciasis 31, 124
 operational research 163
 oral rehydration solution 34
- Pakistan 41
 Pan African Bioethics Initiative (PABIN) 109
 participants, research
 belief systems 41–2
 benefits to 78, 79, 91, 115, 131
 compensation for injury 116–17, 153–4
 consent *see* consent
 continuing care 10, 61, 103, 113–21, 142–3
 decision making by 43–6
 illness developing in 8, 96, 139
 inducements 71, 78–80, 103, 136, 178–9
 information for 43, 60–1, 71–5
 motivations 45–6, 78, 136
 post-trial surveillance 116–18, 142–3
- therapeutic misconception 46
see also control groups
 payments
 as inducements to participate 78, 146
 to members of research ethics committees 105
see also fees
 pharmaceutical companies 27
 drug development 32–3, 34–5
 ethical guidance 65
 fees to research ethics committees 106
 free/subsidised medicines 31, 33–4, 124
 overseas research by US 23, 24
 post-trial responsibilities 121, 123, 124, 142, 180–1
 research priorities 28–30
 scientific review of proposed research 102
 Pharmaceutical Research and Manufacturers of America
 (PhRMA) 22, 23, 24
 pharmacogenetics 33–4
 Philippines 79
 physicians *see* doctors
 placebo 71, 163
 controlled trials 8, 61, 62
 defined 7
 explaining 75
 policy-makers 122
 post-trial issues *see* completion, study
 poverty 131
 power imbalances
 developed/developing countries 29–30, 52, 107, 131
 doctors and patients 42
 see also exploitation, avoidance of
 praziquantel 34, 92
 pregnancy
 antiretroviral therapy 8, 93, 117, 122, 124
 place of confinement 43
 preventive studies
 care of participants 8, 96
 long-term surveillance after 117–18
 priorities, research 24–30, 132–3, 177
 ethical review 102, 140
 external sponsors 27–8, 131
 pharmaceutical companies 28–30
 recommendations 30, 132–3
 setting national 24–7, 30, 132–3
 privacy 73
 private healthcare 94
 proportionality, inducements 80
 proxy, consent by 76–7
 publication, research results 57
 Public Citizen 32, 60
 public meetings 43, 74, 123
 public-private partnerships
 defined 27
 global (GPPPs) 23, 27, 32
- quinine 33
- radio 74
 randomisation 75
 refusal to participate 77–8, 136
 regional fora for developing capacity for ethical review 108, 109
 relativism, moral 51–2, 134
 religious representatives, research ethics committees 105
 remuneration *see* payments
 research
 needs 5–6
 types 24, 25–6, 163
 researchers
 implementation of guidance 59
 post-trial responsibilities 113, 116, 117–18, 122–3, 125,
 141–3
 standards of care provided 90–1
 resources
 to conduct research 22
 healthcare, variations between countries 17–21
 inequitable distribution 15, 49
 respect for persons 51, 57, 133–4
 conflicts 77, 90, 135

- respect for persons (*continued*)
 - consent and 71
 - standards of care and 137–8
- results, research
 - implementation 9–10, 113, 119–25, 142–3
 - reporting and publication 57, 123
- risks, research
 - giving information on 75
 - level of inducements and 79, 80
 - limiting legal liability 81
 - see also* adverse effects
- river blindness 31, 124
- Russia 104, 109

- safari research 126
- salt, iodination 123
- sanitation 21
- schistosomiasis 34, 92
- scientific principles 57
- scientific validity, review 102, 140, 167
- screening, cancer 25, 89
- Senegal 117–18
- sexual behaviour, high-risk 25
- sexually transmitted diseases (STDs) 95, 97
- shamans 40, 42, 43
- side-effects *see* adverse effects
- sleeping sickness 25
- social context 39–46, 72–3, 133
- social research 25, 163
- socio-economic context 15–35, 132
- South Africa
 - national guidance 115, 126, 151, 152, 156
 - women 45, 77–8
- South-East Asia 91
- Special Programme of Research, Development and Research Training in Human Reproduction 108
- Special Programme for Research and Training in Tropical Disease (TDR) 27–8, 108, 121, 154
- spirits, affliction by 40–1
- sponsors, research 6, 27–8
 - funding research ethics committees 106–7
 - post-trial responsibilities 113, 116, 117–28, 123–5, 141–3, 180–1
 - priorities 27–30, 131
 - scientific review by 102
 - standards of care provided 90–1
 - see also* externally sponsored research; pharmaceutical companies
- standards of care 7–8, 87–97, 137–9
 - appropriate 89–92
 - consultation views 179
 - ethical review 103
 - guidance 57, 61, 87–8, 96, 152–4
 - importance of context 92–4
 - national 94–5, 138–9
 - non-universal 89, 94–7, 137
 - in preventive studies 96
 - recommendations 94–5, 96, 97, 139
 - universal 89, 92–4, 137
 - unrelated illnesses 97, 139
- Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) 108
- subjects, research *see* participants, research
- suffering, alleviation of 50, 51, 57, 90–1, 133–4
- surveillance *see* monitoring

- Tanzania 25
- Task Force on Health Research for Development 26, 30
- 10/90 disequilibrium 21–2
- tetanus, neonatal 122
- Thailand
 - ethical review 109
 - HIV 7, 25, 93–4
 - motivation of participants 45
 - national guidance 151
 - research priorities 27
- therapeutic misconception 46
- therapeutic research 61, 71

- trachoma 26, 31
- traditional healers 40, 133, 178
 - client relationships 42–3
- traditional medical systems 39
 - combined with modern healthcare 40
- training
 - in equipment maintenance 126, 143
 - in information provision 74
 - in interpreting/applying guidance 65–6, 134–5
 - members of research ethics committees 105, 108–9, 141
 - in research expertise 22, 125–6, 131–2, 143
 - see also* expertise, developing local
- treatment
 - best current method 88–9, 93–4
 - conditions arising during study 91
 - as inducement to participate 79
 - research incorporating 61, 71
 - standards *see* standards of care
 - see also* healthcare; interventions
- Trypanosoma brucei rhodesiense* 25
- tuberculosis (TB)
 - prophylaxis 95
 - research funding 27, 28, 30
- Tufts Center for the Study of Drug Development 32

- Uganda
 - consent 44
 - ENHR strategy 26
 - HIV 25, 124
 - national guidance 63, 115, 120, 151, 152, 155, 156
 - sleeping sickness 25
- Ukraine 104
- umbilical cord care 41
- UNAIDS *see* Ethical Considerations in HIV Preventive Vaccine Research
- UNESCO 58, 71
- UNICEF 122–3
- United Kingdom (UK)
 - national guidance 150, 151, 152, 153, 155
 - research funding 27, 28
- United Nations 58
- United Nations Population Fund (UNFPA) 25
- United States (US)
 - consent 71
 - healthcare expenditure 20
 - infant mortality rates 17
 - national guidance 63–4, 150, 151, 152, 156
 - research overseas 22–3, 27
- unsafe practices, avoiding 91–2
- urine samples 41

- vaccines 5
 - care of study participants 8, 96, 119–20
 - cerebro-spinal meningitis 8
 - costs 34
 - development of new 32
 - donated/subsidised 31, 124
- VaxGen 25
- Venezuela, leprosy study 7
- video tapes 74
- Vietnam 65
- violence, domestic 82
- vitamin A supplements 31
- vulnerable populations
 - avoidance of exploitation *see* exploitation, avoidance of
 - ethical issues 169
 - levels of inducement 80
 - represented on research ethics committees 105

- water 21
- Wellcome Trust, The 23, 27, 29
- withdrawal, study 78
- witnessing verbal consent 82, 83, 137
- women
 - decision making by 44–6, 71, 77–8
 - on research ethics committees 105

- World Health Organization (WHO) 179
disability-adjusted life expectancy 16
research guidelines 58, 62
research priorities 24–6
see also CIOMS/WHO guidelines; Guidelines for Good
Clinical Practice for Trials on Pharmaceutical Products
- World Medical Association (WMA) 58
Helsinki Declaration *see* Helsinki Declaration
- World Trade Organisation (WTO) 33
- Yunani system 39
- Zentel 30
zidovudine, for pregnant women 8
Zimbabwe, cervical cancer screening 25
Zithromax (azithromycin) 26, 31

Genetic screening: ethical issues

Reprinted October 1997

Human tissue: ethical and legal issues

Published April 1995

Animal-to-human transplants: the ethics of xenotransplantation

Published March 1996

Mental disorders and genetics: the ethical context

Published September 1998

Genetically modified crops: the ethical and social issues

Published May 1999

**The ethics of clinical research in developing countries:
a discussion paper**

Published October 1999

Stem cell therapy: the ethical issues – a discussion paper

Published April 2000

Published by

Nuffield Council on Bioethics

28 Bedford Square

London WC1B 3JS

Telephone: 020 7681 9619

Fax: 020 7637 1712

Internet: www.nuffieldbioethics.org