

Research with children: ethical processes and challenges around the world

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Introduction

On 3-4 March 2016, the Nuffield Council on Bioethics hosted an international symposium¹ on children and clinical research with the Global Health Bioethics Network at the Ethox Centre, University of Oxford and the Wellcome Trust Brighton and Sussex Centre for Global Health Research.

The symposium brought together delegates from a dozen middle and low income countries, with experience of working in many more. The aim of the event was to explore further how the conceptual recommendations of the Council's 2015 report Council's report *Children and clinical research: ethical issues*² might be understood or nuanced in very different settings from the UK, and what practical implementation in those settings might look like.

Many of the delegates had circulated accounts of the situation regarding children's participation in clinical research in their country before the meeting, highlighting both the situation with respect to national regulation governing the permissibility of clinical research with children, and the particular challenges experienced in their own practice.

This document is an edited compilation of these accounts, revised since the symposium to reflect on some of the common themes that emerged.

¹ A report of the symposium is available at: <http://nuffieldbioethics.org/wp-content/uploads/Report-of-international-symposium-on-children-and-clinical-research.pdf>

² Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues*, available at: <http://nuffieldbioethics.org/project/children-research/>

Conducting research involving children in the Kingdom of Cambodia (specifically at the Angkor Hospital for Children)

- Claudia Turner

Angkor Hospital for Children

Angkor Hospital for Children (AHC) is a paediatric hospital offering free primary and specialty health care services to children in Siem Reap, Cambodia. Since 1999, AHC has provided more than 1.5 million treatments to Cambodia's children, with more than 180,000 in 2015.

Angkor Hospital for Children is highly desired as a research site because of the high number of patients seen, the variety of conditions, the ease of geographical accessibility and access to the community. We receive more than 60 requests annually to conduct research within the organisation. There is a desire by management for high quality research to be conducted within the organisation and AHC's second strategic goal states that AHC will become a centre of excellence for education and research within Cambodia by 2020. Consequently, in 2015 the AHC Research Committee (AHC RC) was founded. The committee was responsible for defining the research agenda for the organisation:

“Angkor Hospital for Children’s research focus is on clinical paediatric or operationally relevant research that is relevant to the Cambodian population. In addition, AHC is committed to educational research and aiding staff to develop research skills.”

The AHC RC developed a research policy for the organisation and screens all research requests. The screening process looks at feasibility, whether the study fits with the organisational research agenda and resource impact on the organisation. If the AHC RC approves the study it is submitted for ethical review (Table 1).

Table 1. Ethical review for different study types

Project type	**Ethical review
Interventional study	Cambodian National Ethics Committee AHC Institutional Review Board
Study involving patient contact or samples	Cambodian National Ethics Committee AHC Institutional Review Board
Community based studies	Cambodian National Ethics Committee AHC Institutional Review Board
Retrospective studies	AHC Institutional Review Board
* Organisational studies	AHC Institutional Review Board
* Educational studies	AHC Institutional Review Board
* Surveillance	AHC Institutional Review Board

* *Within the hospital*

** *AHC research committee reserve the right to request further ethical review*

AHC Institutional Review Board

The organisational institutional review board (IRB) has been operating in its current form since 2013. There are ten members (five AHC clinical staff, three AHC non clinical staff and two lay members). Initial training in GCP and ethics was conducted by Dr Phaik Yeong Cheah (MORU). The IRB meets on an *ad hoc* basis, approximately once every two months. Principal investigators are encouraged to attend. The team use a checklist against which they determine whether a study is “ethical” ([Appendix 1](#)).

Cambodian National Ethics Committee

The Cambodian National Ethics committee was first formed in 2002. The committee is based within the National Institute for Public Health and meets every 2–3 months. Members are mostly from the medical profession. It is difficult to find out how the review process is actually conducted.

Future plans for research at Angkor Hospital for Children

Plans moving forwards are to get research formally recognised as an AHC organisational activity with the Cambodian Ministry of Health.

Angkor Hospital for Children are in the process of setting up a young persons’ advisory group with the aim of giving young people a voice in their healthcare provision and research that is conducted within AHC.

Cambodia: appendix 1 – check list for AHC IRB ethical approval

Angkor Hospital for Children IRB#1 - Protocol Review Standards

Protocol:

Principal investigator:

Requirement	Comments for IRB discussion
1. Study design is scientifically sound and will not expose subjects to unnecessary risk.	Is the hypothesis clear and clearly stated?
	Is the study design appropriate to prove the hypothesis?
	Will the research contribute to useful knowledge?
2. Risks to subjects are reasonable in view of possible benefits.	What is the level of risk? Minimal, Moderate, High, Unacceptable
	What are the types of risk? Physical, Psychological, Social, Economic
	Are the risks clearly stated in the protocol?
	Is there direct benefit to subjects?
	Are the risks reasonable in view of possible benefits to subjects and /or importance of knowledge?
3. Subject selection is appropriate?	Who is to be enrolled?
	Are there inclusion and exclusion criteria?
	Are these subjects appropriate for the protocol?
4. Is there protection for vulnerable subjects?	Is there protection for vulnerable subjects, e.g. mentally or physically disabled?
5. Is there maximum subject safety?	Does the study design minimise risks to subjects?
6. Is there privacy and confidentiality for subjects?	How will personally identifiable data be protected from general access or use?
	Are there any special privacy and confidentiality issues-e.g. genetic data, HIV?

Additional considerations

1. Collaborative research	Are there other institutions involved in this research?
	Have other IRBs approved this research?
2. Subject compensation	Do subjects receive appropriate amounts of money for expenses or compensation?

Requirements for informed consent

A statement that the study involves research	
An explanation of the purposes of the research	
The expected duration of the subject's participation	
A description of the procedures to be followed	
Identification of any procedures which are experimental	
A description of any risks or discomforts which may occur	
A description of any benefits to subjects or others	
Mention of any alternative procedures which may be of benefit to the patient	
A description of methods to maintain confidentiality	
If the risk is more than minimal, statement about treatment and compensation if injury occurs	
Explanation of whom to contact for answers to questions about research, subjects' research and in case of research-related injury	
Statement that participation is voluntary, there will be no penalty if subject refuses to participate and the subject may withdraw from the study at any time without penalty.	

A statement that the research involves risks	
Explanation of any circumstances when the subject's participation may be terminated by the investigator without asking the subject's consent	
Explanation of any additional costs to the subject e.g. transport, time away from work	
Explanation of the consequences of the subject's withdrawal from the research	
A statement that results affecting the subject will be given to him/ her	
The approximate number of subjects	
Amount of payments available, required conditions for payment, schedule of payments and procedure for early subject withdrawal	
If samples could lead to development of a commercially viable product, inclusion of the following statement: I authorise the use of my bodily fluids, substances or tissue in this research. It is possible that commercially profitable products may someday be developed from these samples. There are no profits to share any profits from such products with any of the research subjects.	

Other comments:

Major issues preventing approval:

Signed:

Date:

.....

Human Protections Administrator
Angkor Hospital for Children IRB#1

Young Lives: experiences of seeking ethics approval: Ethiopia, India (Andhra Pradesh), Peru and Vietnam

- Virginia Morrow, Deputy Director, Young Lives³

Background

Young Lives is a longitudinal cohort study of 12,000 children, in four countries (Ethiopia, India, Peru and Vietnam) over 15 years, 2001-17, and includes:

- Young Lives surveys with children, including a number of instruments administered by fieldworkers using CAPI, cognitive tests, and a self-administered questionnaire (SAQ) that is completed, put in an envelope and handed to fieldworkers
- Young Lives qualitative research with children
- School surveys – involving Young Lives children and their peers, in school-based tests of children’s competencies

Over the lifetime of Young Lives research, international and national approaches to research ethics approval have changed rapidly. This brief note describes Young Lives experiences of seeking ethics approval from various Research Ethics Committees (RECs) / Institutional Review Boards (IRBs) to date (see: www.younglives.org.uk).

Existing ethics approvals

- Young Lives original proposal (2000/1) was checked against the ethics standards of each of its six original partner institutions, and received approval from the London School of Hygiene and Tropical Medicine ethics committee.
- A pilot phase in South Africa in 2001–2 was given ethical approval by the Rand Afrikaans University, South Africa
- IIN (Instituto de Investigación Nutricional) IRB Peru (since 2002)
- Social Science & Humanities Interdivisional REC (SSH IDREC) University of Oxford (since 2005)
- Hanoi School of Public Health Research Ethics Committee (2015)
- Partner organisation in Hyderabad - research ethics committee (2015)
- Ethiopia College of Health Sciences (2015)

Young Lives seeks ethics approval for each new survey round and any additional elements (e.g. school surveys, qualitative research or sub-study). In 2015, Young Lives sought and received ethics approval from University of Oxford IDREC and each study country for piloting the 5th round of the Young Lives survey, being conducted this year (2016.) Young Lives has received approval for the final survey instruments from University of Oxford IDREC, and in each study country.

³ Thanks to Marta Favara, Pati Espinoza and Graham Bray, Young Lives, Oxford, and Mary Penny, IIN/Young Lives Peru for their help in preparing this note.

1. Ethiopia

Ethics approval was received from College of Health Sciences, Addis Ababa University IRB, for piloting Young Lives survey in 2015. Concerns were raised by the IRB about:

- piloting of some parts of the survey in schools (cognitive tests, psycho-social scales and use of computers and other digital devices, where large amounts of data were needed for IRT analysis)
- needing 'assent' forms for children,
- information and consent forms for parents, representation of Young Lives child participants in the media
- local languages (translations of instruments requested).

Colleges of Health IRB was not felt to be the appropriate body to approve the Young Lives School Survey as it contains no health elements. National guidelines in Ethiopia enable waivers of informed consent if the research project 'carries no more than minimal risk, if the research... is to be conducted or approved by federal or regional government and is designed to study, evaluate, or otherwise explore public benefit or service programs...'. It was felt that this description covers Young Lives School Survey, which anyway requires informed consent from children who participate.

However, it is worth noting that while the IRB approved all the questions in the SAQ, some fieldworkers and respondents found them sensitive and said that they made them feel uncomfortable. This, and the length of the SAQ questionnaire – which took almost an hour to complete because of low literacy rates – meant the SAQ has been reduced to three questions for the 22 year olds, and eight for the 15 year olds (the same questions administered to 15 year olds in Round 3 of the survey).

2. Andhra Pradesh and Telangana, India

We discussed possibilities of seeking research ethics approval in Delhi (via PHF India) but it was felt the process would be too lengthy. Our partner research organisation (where the PI and survey team are based) (re-)constituted their research ethics committee, and gave approval for piloting the survey. However, the REC rejected questions in the SAQ that were felt to be too sensitive and culturally inappropriate to ask of 15-year-olds (and indeed 22-year-olds). These questions related to 'dating', 'romantic relationships' and sexual activities. The REC also wanted to alter the wording of the Gender Equitable Men Scale (GEM) (a scale measuring attitudes toward gender norms in intimate relationships or differing social expectations for men and women) to be gender-neutral rather than women-centric. The REC explained that this was because of internalisation of patriarchal values by both males and females (which was what we wanted to investigate).

The REC were understandably concerned that asking culturally-inappropriate questions could potentially damage long-term relationships within communities and with respondents. The questions were dropped. Further, the SAQ was reduced to two questions for the 15-year-olds (same questions asked to 15-year-olds in the third survey round) and two questions for 22-year-olds.

3. Peru

Since the inception of Young Lives, ethics approval has been provided by the IRB of *Instituto de Investigación Nutricional* (IIN) in Lima, Peru. For piloting R5 of the survey (which took place in schools and colleges as well as households), The IRB required parental consent (signed consent forms from parents) for 15-year-olds to participate in piloting new psycho-social scales. The piloting took place both in households and in schools. The problem with the consent forms delayed the process for piloting in schools / institutions, and meant low participation rates for piloting, and meant visiting more schools than we planned in order to reach the desired sample size (but this will not be a concern in the main survey because the research is undertaken at household level, and informed consent sought from parents and young people). It is worth noting that for the final instruments, Young Lives Peru has five consent forms (for respondents >18), and two assent forms (for respondents <18), all of which include an information sheet about the study.

Also of concern and ongoing discussion in Peru are gifts given at the end of interviews as a 'thank you'. Current plans are to give a gift to the index child and to the mother (or whoever answers the household survey). Small portable radios and batteries that charge a cell phone have been identified as the best option. For the mothers we give plastic storage boxes. In some of the other Young Lives countries, participants receive a day's pay, as is acceptable according to ethics guidelines - 'fair return should be made for help and services' (ASA 2011: p6; discussed in more detail in Morrow 2013). This has not been approved by the IIN IRB.

4. Vietnam

Young Lives PI approached Hanoi School of Public Health IRB for approval for piloting. After some delays (the committee was too busy, or committee members being absent/away) we proceeded with the piloting because arrangements were in place with households and schools / universities. An official letter was provided from the Government Statistical Office explaining that other similar multi-topic surveys including MICS, LMS, DHS, do not seek ethics approval in Vietnam. Eventually, ethics approval was received. The committee requested revisions to the consent form, and there were sensitivities relating to ethnic minorities. Postponing piloting would have been very costly, both financially, and in terms of relationships of trust with our partners. The approval was granted for both the pilot and the final questionnaire. This assumes that the final questionnaire is a reduced version of the pilot version that contained all the possible instruments – however, ethics approval was granted for one year. This means that we will need to apply for an extension.

A brief note about informed consent and 'assent'

Readers may have noted that in the text, I have used the word 'assent' in quotation marks when describing Ethiopia, and assent without quote marks, when describing Peru. The concept of assent is, from a UK perspective, problematic (see Alderson 2012). In Young Lives, we have prioritised 'informed consent' from children themselves to participate in the study, as well as from their parents/caregivers, over children's assent. In some cases, children have refused to participate, despite their parents' consent and this refusal is (of course) respected.

Why is assent a problem? Because it is a potentially weakened form of ‘voluntary, informed consent’ (Nuremberg Code). By 2013, Helsinki altered consent to assent: para 29: ‘When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject’s dissent should be respected.’

‘Assent’ is widely used in US-based clinical research, and can be found in international guidance derived from USA (and which is used in Peru – hence the reference to ‘assent forms’). In US, ‘the consent of parents/guardians to research must be sought ‘at all ages of the child; furthermore, the child’s assent should be sought from the age of 7 upwards’ (see Alderson 2012).

1. Alderson (2012) notes that in USA, it is assumed that children cannot usually give legally valid consent until they are aged 18 or 19, unless they count as ‘mature minors’. The assumption that children cannot consent clashes not only with English law, but also with the spirit of UN CRC Article 12 (note, USA being the only country that has not ratified UN CRC). In English law, children have the right to consent if they are deemed competent. English law influences Commonwealth countries, though the extent to which this is the case in relation to research ethics is not clear – for example it is not the case in Kenya, where: ‘national guidelines require young people’s assent in writing, unless a waiver is given’ (this is in line with US guidelines).

2. Assent is a weak form of informed consent and can be waived or over-ridden, and does not require an **informed** decision. Assent refers to agreement by children who may understand some, but not all, the main issues. It is questionable whether a partly-informed decision can count as a decision at all. This relates to information and the importance of making sure that the decision is ‘informed’. Assent can fail to emphasise information, and can focus on ‘getting a yes’.

3. Assent can mean ‘at least not refusing’. But that can be different from actually assenting. Assent may be misused to cover over children’s unwillingness to participate in a study, or their refusal. (Alderson & Morrow 2011).

As Alderson (2012) suggests, ‘assent has not the power, clarity, or history of consent. ... Assent in US guidance is non-refusal or simple agreement, without the understanding, discretion and legal validity. Informed consent involves a pause before the person makes and signifies the decision, usually by signing a consent form. ... Assent, however, need not involve that formal moment of choice and statement’. Further, the notion of ‘non-refusal’ is problematic and not a positive decision to participate.

Cross-cultural factors – how does ‘informed consent’ and ‘assent’ translate into other languages?

Young Lives works in several languages and dialects. I asked researchers for translations of the words ‘consent’ and ‘assent’ into Spanish, Amharic, Afar Oromo, Hindi and Telugu, what they understood by the terms ‘informed consent’ and ‘assent’. In lay English, for a native English speaker, the differences between consent and assent are by no means self-evident. Consent = (verb) – to express

willingness, agree. Noun: - voluntary agreement, compliance, permission. Assent = (verb) - consent, to express agreement. Noun: official sanction, acceptance (Concise Oxford Dictionary). The difference between the two is subtle, and not recognised in Spanish (*consenter, asentir*) nor in Telugu.

Simiminet (Amharic) means agreement (noun) and *mesmamet* (Amharic) to agree (verb); both have the connotation of two parties agreeing. Another possible word would have been *fiqad*, literally permission and the verb *mefqed* literally allowing or giving permission and meaning giving consent.

In Oromo, *wali galtee* - (noun) meaning agreement - the prefix *wal* means together (the dictionary calls it a prefix for reciprocal action or combined subjects, and *galtee* is entering, and the Gragg dictionary has it as *Wali gala v agree, approve, stick together*).

The word 'assent' was not really recognised by our Ethiopia team. In Hindi, there is a small but subtle distinction, rather like English: [सहमति](#) (f) [sahamati] means 'to agree'; [अनुमति](#) (f) [anumati] means 'to permit'. All team members (Ethiopia, India, Peru, I was not able to ask Vietnam) recognised and worked with 'informed consent', the emphasis being on 'information' and 'consent'. (I felt it was confusing and somewhat unfair, to even ask them to consider the meaning of the word 'assent'.)

A recent blog by Stefania Maggi, a researcher at Carleton University in Ottawa, suggests the following change to consent processes in research with children: <http://childethics.com/forum/small-change-great-implications/>

Here is a typical statement in parental consent forms for children of all ages:

"As parent or legal guardian, I authorize (child's name) to become a participant in the research study described in this form."

Of course many variations of this wording exist, but the bottom line is that parents are asked to consent for their child to participate in research. Try and use this instead:

"As parent or legal guardian, I give permission to the research team to approach my child (name of the child) and ask if he/she wishes to participate in your project."

In this version of parental consent, parents are asked permission to talk to the child and ask him/her if he/she wishes to participate in the study.

Alderson & Morrow (2011) and copious other guidelines emphasise that children should be asked to give informed consent.

British Psychological Society Guidelines (2009) state: 'The consent of participants in research, whatever their age or competence, should always be sought. For children under 16 years of age and for other persons where capacity to consent may be impaired, the additional consent of parents or those with legal responsibility for the individual should normally also be sought. In special cases such as where it may be important that views of such participants about them should not be suppressed, the rationale for not seeking

parental consent should be clearly stated and approved by a REC'.

It is good practice to seek permission from everybody involved, and a parent/caregiver may feel upset and disrespected when they have not been informed, consulted, or given permission), but children's informed consent is paramount (in reality, one would not expect to get good quality data if children take part in research without consent or understanding, or against their will). In the case of very young children, then parental consent is the main requirement, and research teams explain the study, what they are trying to find out, and why. Young Lives collects basic anthropometric data from babies/children of the Young Lives participants, and informed consent is sought from both parents where possible, and, in India, from in-laws, where appropriate.

Intergenerational factors – when children know more than parents

There is a further point to make about literacy and obtaining informed consent when children are literate and parents/caregivers are not. In Young Lives experience, especially in India and Ethiopia, parents may not be able to read or write, and children actively support their parents via the literacy skills they have gained at school. In Ethiopia, particularly, parents see their children as knowledgeable and 'expert' because they can read and write, and have basic education. In India, young people assist their parents to complete forms in order to access social protection/financial support from government schemes.

The assumption in much guidance is that 'children cannot consent' but the rapid pace of modernisation, and expansion of schooling (admittedly of variable quality) means that children are likely to have (perhaps) more exposure to and understanding of research, enquiry, finding out things, projects, even laws and social policy, and sources of support, than their parents.

Lessons learned:

- (i) Country experiences differ greatly, but acquiring ethics approval is feasible.
- (ii) It takes time for ethics committees to meet and make decisions - it is advisable to allow a minimum of at least three months - and to plan ahead.
- (iii) In our experience, national/local ethics committees tend to be focussed on clinical/ medical research, especially clinical trials.
- (iv) Broad social science research ethics committees are not well-established yet in low and middle-income countries, nor available, though this is changing rapidly.
- (v) Existing ethics committees in low and middle-income countries as yet have little experience in observational research, i.e. not a (clinical) trial - research that does not involve an intervention, randomisation and placebos; and minimal risk research, i.e. research that involves activities that are no more risky than everyday activities. Social science research usually falls into these categories.

- (vi) There are complexities in reconciling requirements of five different ethics committees in a multi-country study – a balance has to be struck in retaining comparability of instruments.
- (vii) Seek local advice, seek informed consent from everyone involved, and check understanding frequently. If researchers are required to work with the concept of 'assent', then care needs to be taken to explore the meaning of the term in context. Working in translation makes 'assent' a concept that difficult to operationalise in other languages, let alone in English.

References / resources:

Alderson, P. (2012) Children's consent and 'assent' to healthcare research. In Freeman, M., (ed) *Current Legal Issues, Vol; 14: Law and Childhood Studies*. Oxford: Oxford University Press.

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Alderson P, and Morrow V (2011) *The ethics of research with children and young people: a practical handbook* (London: SAGE Publications)

Morrow, V. (2009) The ethics of social research with children and families in Young Lives: practical experiences. *Working paper No 53*, Young Lives, Oxford.

ESRC Framework for Research Ethics: www.esrc.ac.uk/researchethics

Young Lives case study: www.esrc.ac.uk/funding/guidance-for-applicants/research-ethics/ethics-case-studies/case-study-informed-consent-working-with-children-internationally/

UNICEF Office of Research: www.childethics.com

Kenya notes on ethics review processes and challenges experienced

- Vicki Marsh, Sassy Molyneux and Dorcas Kamuya

National Science and Ethics Review processes for research involving people

In Kenya, the National Commission for Science Technology and Innovation (NACOSTI) is the state appointed commission with the mandate to promote, coordinate and regulate the progress of Science, Technology and Innovation in the country. NACOSTI was established through the Science, Technology and Innovation Act 2013, repealing an earlier 1979 Act and has overall responsibility for accrediting and monitoring science and ethics review processes for all research in Kenya, including research involving people. This includes accreditation and monitoring of Institutional Review Boards (IRBs) at state and non-state universities, referral hospitals, and other institutions that undertake research, including the Kenya Medical Research Institute (KEMRI). For clinical trials in Kenya, the National Medicines Regulatory Authority (Pharmacy and Poisons Board) must also review and approve research protocols.

[KEMRI](#) is a State Corporation established through the Science and Technology (Amendment) Act of 1979 as a national body responsible for carrying out health research in Kenya. KEMRI's institutional review body, the Science and Ethics Review Unit (SERU), is accredited by NACOSTI to undertake science and ethics review processes, as part of its overall mandate. Across each of KEMRI's 11 research centres in Kenya, Centre level governance committees review and approve new research protocols before forwarding to SERU for national level approval.

For international collaborative research, or where international funders are involved, review processes may also involve Ethics Review Committees outside Kenya. For example, the KEMRI Wellcome Trust Research Programme (KWTRP) is an international collaborative programme involving KEMRI, the Wellcome Trust and Oxford University, and is hosted at one of the KEMRI centres. In addition to approval from SERU, protocols developed at KWTRP are often reviewed by ethics committees at Oxford University, other collaborating universities and/or a range of different international funding agencies.

Challenges for health research involving children and young people in KWTRP, Kilifi, Kenya

(From researchers' experiences of research review processes and a recent community/student consultation)

- Challenges experienced in accessing health care through often over-stretched public health services can have a major effect on community perceptions of the acceptability of research that includes the provision of health care: children's parents may often agree to studies in order to access that health care, as

opposed to out of a strong interest to be involved in the research.⁴ While this factor affects research involving adults and children, children are particularly affected given their higher rates of morbidity and uptake of public health services.⁵

- Unfamiliarity with health research and science is common in many areas of Kenya, including through limited exposure to formal education. This unfamiliarity includes low awareness of regulatory systems for science and research ethics, contributing to unrealistic fears and hopes about participation. While clearly relevant to all types of clinical research, not just that involving children, this phenomenon has a major influence on the acceptability of research involving children. In relation to ‘familiarity’, we note the importance of ensuring that parents place neither too much nor too little trust on researchers in making decisions about children’s involvement in research.⁶
- Parents and young people have particular concerns about involving young children in research. Children are seen as special in relation to their need for parental protection and support, linked to a fragility associated with immaturity and their potentiality. But there is also an understanding that research involving young children is important if illnesses that affect this age group are to be tackled.
- Most people see that children and young people should be increasingly involved in making decisions about their own involvement in research as they get older, but this is also dependent on the type of research (easier for younger children to have a say about their participation in lower than higher risk research); the personality of the child and parents; the normal life experiences of the child – particularly the types of decisions they make and responsibilities they carry in everyday life; and their exposure to formal education. Given the many personal and contextual influences on the rate at which control is seen to shift, it is difficult for researchers to assess how much/how children and young people should be involved in decision making about research.
- In relation to age, overall, parents and young people recognise a gradual shift of control over decision-making from parents to young people with maturity, without clear ‘cut off’ age groups. This also applies to research decisions. In situations where children and young people have had greater access to formal schooling and digital media than their parents, there is likely to be a faster shift towards young people making independent decisions.
- There is a lack of clarity in how researchers should approach young people for consent for research on sensitive topics (e.g. around sexual behaviour or recreational drug use) and their parents’ role. Kenya guidelines on HIV/AIDS

⁴ Also see: Molyneux S, Mulupi S, Mbaabu L, and Marsh V (2012) Benefits and payments for research participants: experiences and views from a research centre on the Kenyan coast *BMC Medical Ethics* **13(1)**: 13.

⁵ This situation generates particular responsibilities for researchers in developing partnerships with government health authorities to support long term care and capacity development, building effective community engagement to strengthen understanding of research and finding reasonable ways to contribute to structural inequalities that underpin low access to health care.

⁶ Also see: Molyneux C, Peshu N, and Marsh K (2005) Trust and informed consent: insights from community members on the Kenyan coast *Social Science & Medicine* **61(7)**: 1463-73; Molyneux S, and Bull S (2013) Consent and community engagement in diverse research contexts: reviewing and developing research and practice: participants in the community engagement and consent workshop, Kilifi, Kenya, March 2011 *Journal of Empirical Research on Human Research Ethics* **8(4)**: 1-18.

research⁷ recognises these challenges and specifies situations where SERU can give a waiver of parental consent, but these are difficult situations for researchers to understand how to manage in local communities.

- In contrast to regulations in the UK, there is a perceived importance of *both* parents being involved in making decisions about their child participating in research, and challenges in gaining consent where many fathers work away from home but carry traditional paternal responsibilities for control of domestic resources that limits mothers' independence.
- Gender and religion can influence community perceptions of the acceptability of, and decision-making for, research involving children and young people. In some situations mothers and young women may need particular support from researchers/consent processes to ensure that their views are heard and respected.⁸
- Approximately 270,000 children and young people were described as 'double orphans' in 2012 in Kenya, presenting many challenges in setting up fair ways of conducting much needed research in this population.⁹
- Complexities in applying regulatory standards 'on the ground': KEMRI SERU require that children and young people aged 13 years and over should sign assent forms as part of a consent process, whereas researchers' experience on the ground suggests that this may be a worrying experience for young people.
- In Kenya, many young people attend boarding schools at secondary level (from about 13 or 14 years) far from home. Seeking assent and consent from the young person and their parent(s) can be practically challenging for researchers. It is not clear how these processes should work for older children (e.g. 16+) particularly for low risk research (e.g. questionnaire surveys).
- It is not clear how research staff responsible for consent/assent processes should be trained and supported – the skills for communicating well with children, young people and parents, including as a group, are clearly specialised.

⁷ National AIDS and STI Control Programme (NASCOP) Ministry of Health Government of Kenya and Kenya Medical Research Institute (KEMRI) (2015) *Guidelines for conducting adolescents sexual and reproductive health research in Kenya*, available at: <http://www.maishamaarifa.or.ke/admin/Content/Uploads/downloads/national-guidelines-for-conducting-adolescent-hiv-sexual-and-reproductive-health-research-in-kenya.pdf>.

⁸ Also see: Kamuya DM, Theobald SJ, Marsh V *et al.* (2015) "The one who chases you away does not tell you go": silent refusals and complex power relations in research consent processes in Coastal Kenya *PLoS ONE* **10(5)**: e0126671.

⁹ Lee VC, Muriithi P, Gilbert-Nandra U *et al.* (2014) Orphans and vulnerable children in Kenya: results from a nationally representative population-based survey *JAIDS Journal of Acquired Immune Deficiency Syndromes* **66**: S89-S97.

Mahidol Oxford Tropical Medicine Research Unit, University of Oxford

- *Phaik Yeong Cheah*

Background

Based in Bangkok, the Mahidol Oxford Tropical Medicine Research Unit, has been conducting tropical medicine research in adults and children for more than 30 years in Southeast Asia, South Asia and Africa. At any one time, the Unit has around 60-70 active clinical studies, of which many *do not exclude* children. In addition, we have conducted a number of large paediatric specific studies: for example, we recruited 5,425 children with severe malaria in a pan-African study (Dondorp et al, 2010); our study in the Democratic Republic of Congo recruited more than 600 children with uncomplicated malaria (Onyamboko et al, 2014); and we have many studies in a paediatric hospital in Cambodia.

Challenges in paediatric research

Regulatory challenges

- E.g. how can we ethically develop drugs for severe malaria in children when there is a declining number of adults with severe malaria?
- Risk of exclusion of older children in research (those who cannot consent for themselves)
- No (obvious) paediatric regulations e.g. Laos, Cambodia
- Inconsistency – between regulations and ethics committee requirements and between different ECs e.g. Thailand - written assent for those under seven, co-consent for those aged 7-18 in addition to parental consent for research *but* medical majority is 20 years' old
- Problems with illiteracy for many communities e.g. near the Myanmar border
- Problems with *written* consent/assent
- Extra challenging in multicentre studies as regulations differ from country to country

Decision making: consent and assent

- Lack of formal education and low health literacy, hierarchical societies, culture of collectivism
- Valid consent for parent / guardians?
- Who is the parent/guardian? Concept of *legal* guardian may not exist
- Older children – some can *ethically* consent for themselves but not *legally* as they have not reached majority

Lack of expertise in paediatric research

- Ethics committee, researchers and clinical research staff
- Ethics committees afraid to approve paediatric studies
- Because there are so few studies, ECs do not regularly review protocols on paediatric research

What constitutes a fair offer

- Close relationship between research and clinical care, therapeutic misconception, issues of standards of care

Brief summary of ethical-legal framework for child research in South Africa

- Ann Strode (PhD)¹⁰, Catherine Slack (PhD)¹¹

Introduction

South Africa has a well-established ethical-legal framework for regulating health research. It is based on an institutional framework comprising the National Health Research Ethics Council (NHREC), institutional Research Ethics Committees (RECs), a National Health Research Committee (which establishes research priorities) and a national drug regulatory authority, the Medicines Control Council (MCC) (Strode, 2013). There are also legal norms detailing how and when health research may take place - these are largely found in section 71 of the National Health Act of 2003 (hereafter s71 of the NHA) which was operationalised on 1 March, 2012 (*Government Gazette*, 2012; Strode, Richter, Wallace, Toohey & Technau, 2014). On the 19th September 2014, these norms were supplemented by more detailed regulations issued by the Minister of Health for health research with human participants (*Government Gazette*, 2014). Table 1 below, provides an overview of this framework.

Table 1: overview of South African ethical-legal framework regulating health research

Health research – research which contributes to knowledge in various health-related fields	
<p>All health research must:</p> <ul style="list-style-type: none"> • Fit within national health research priorities (if undertaken by the public sector) • Comply with ethical norms set by the NHREC (e.g. national guidelines) • Be submitted for ethical review 	
Health research which includes ‘research or experimentation on a living person’	Health research which forms part of a ‘health service for research or experimental purposes’
<p>All health research with human subjects must be with:</p> <ul style="list-style-type: none"> • Written consent • Adherence to prescribed obligations 	<p>All health research which forms part of a health service can only be undertaken if:</p> <ul style="list-style-type: none"> • The user is informed that the health service is experimental • Consent has been obtained from the user, their healthcare provider, the head of the health establishment and the REC

Source: Strode, 2014

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The NHA (2003) gives the NHREC the authority to issue national ethical guidelines which must be used to guide the deliberations of RECs during the ethical review process. There are national ethical guidelines (Department of Health, 2015) and Good Clinical Practice guidelines (Department of Health, 2006) – the latter are currently being revised.

The regulation of health research with children

There are a number of child specific *legal* norms governing health research with children. These are primarily set out in section 71 of the NHA (National Health Act, 2003) and regulations. These norms impact health research with human participants involving ‘minors’ and includes persons under the age of 18. Table 2, below describes these norms.

Table 2: overview of legal norms regulating health research with children in s71

If the health research is considered therapeutic and it enrolls minors it must:

- Be in their best interests
- Obtain consent from parent/guardian and minor themselves if they have understanding

If the health research is considered non-therapeutic and it enrolls minors it must:

- Obtain consent from Minister of Health
- Obtain consent from parent/ guardian, and minor themselves if they have understanding

Source: Strode, 2014

According to s71, there are different obligations depending on the classification of the study and children always require assistance from their parents or legal guardians. The latter norm has been criticised as being overly restrictive (Strode et al., 2014) and conflicts with norms in current ethical guidelines that allow alternative consent approaches for child research depending on certain factors (DoH, 2015). According to regulations, therapeutic research is defined as being research ‘*that holds out the prospect of direct benefit to the participant*’ (Government Gazette, 2014), whilst non-therapeutic research is defined as ‘*research that does not hold out the prospect of direct benefit to the participant but holds out the prospect of generalizable knowledge*’ (Government Gazette, 2014). The ‘best interest’ of the minor is defined as ensuring that ‘significant decisions affecting a minor’s life should aim to promote, amongst others, the minor’s physical, mental, moral, emotional and social welfare’ (Government Gazette, 2014). This places an obligation on RECs reviewing child research that holds out the prospect of direct benefit to consider the degree to which *various domains of welfare* might be promoted by the study (Strode, 2015). The authority to grant ministerial consent for non-therapeutic research with minors has been delegated to RECs that are fully registered with the NHREC. The *ethical* norms for health research with children are largely in line with the legal principles set out above, with some exceptions. For example, the national ethical

guidelines offer more flexibility regarding possible consent strategies that may be used (Strode 2015). A summary of the ethical norms for research with children is set out in Table 3 below.

Table 3: norms for child research set out in national ethical guidelines (DOH 2015)

The participation of children is indispensable for the research
The research problem is of relevance to children
Taking part would not be contrary to the best interests of the child [new]
The research presents acceptable standards of risk for child participants
The research will take into account children's privacy interests [new]
The research will ensure abuse and neglect are reported [new]
The research will ensure thoughtful reporting of underage sex [new]
The research will seek appropriate permission for the research (consent from parent or guardian, or from a substitute; or from children themselves are possible approaches depending on various factors)
The research will be reviewed by an REC with appropriate child expertise

Source: Slack 2015

Resources

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Engaging and involving young people in biomedical and health-related research in the UK

- *Bella Starling*

Engagement and involvement

My area of specialism is public engagement with research, which comprises a spectrum of activities from science communication to an active partnership in research between people and researchers. Engagement can be defined as “... *the myriad of ways in which the activity and benefits of higher education and research can be shared with the public. Engagement is by definition a two-way process, involving interaction and listening, with the goal of generating mutual benefit*” ([National Coordinating Centre for Public Engagement](#)); involvement can be defined as “*where members of the public are actively involved in research projects and in research organisations.*” (INVOLVE <http://www.invo.org.uk/>)

Some would argue for a clear distinction between engagement and involvement; however, it can also be argued that engagement and involvement operate on a spectrum of activities, that effective research needs both engagement and involvement, and that engagement and involvement are co-dependent. Engagement and involvement should be seen as different from participation, where people take part (are subjects) in a research study.

Engaging young people in research

My work does not exclusively focus on young people, however I do have significant experience of working with young people, mostly in the 11-17-year-old age range and so my comments reflect experiences with these ages.

Schools

Research and the research process features in many places in the National Curriculum for schools, usually as part of the science curriculum, but also in, for example, the PSHE (personal, social, health and economic) curriculum. While the teaching of science in schools remains largely facts-based, some education and examination boards have developed approaches that focus on the process of science (e.g. [‘How science works’](#)) and on the social and ethical aspects of science (e.g. Science Key Stage 3 Programme of Study – for 14-16-year-olds).

Several initiatives support the teaching of science and research in schools, including the [Schools-University Partnerships Initiative](#) (SUPI) which supports universities to work in partnership with local schools to develop more effective engagements between researchers and pupils.

Our experience of supporting the science curriculum through hands-on activities (e.g. DNA workshops for 14-18-year-olds) suggests that:

- Ethical and social considerations are an effective ‘hook’ to engage school pupils with research;

- ‘Hands-on’ experiences are greatly appreciated by both teachers and students, as a good ‘way in’ to enthuse young people about research, particularly at a time when hands-on activities are becoming less prioritised in schools;
- Very few young people are aware of careers in science perhaps reflecting a low awareness of research processes amongst school students; gender-stereotyping remains prevalent in science careers ([Wellcome Monitor 2013](#)).

Informal science learning, engagement

The UK has a vibrant culture of stimulating science learning outside of schools, e.g. through science festivals, museums, social media etc. supported through organisations such as the [Wellcome Trust](#), learned societies and science organisations (e.g. the British Science Association).

Our experience of informal science learning projects suggests that:

- Place for engagement is important – more effective engagement with young people (and people generally) happens when the engagement ‘goes to’ young people, rather than expecting young people to ‘come to’ the engagement;
- Knowing your audience is key – especially with young people, understanding the age range, special circumstances and/or vulnerabilities of your audience is important and will result in different types of engagement and activities;
- Methodology – using alternative media, such as film, social media, performance can create effective engagement. Different media can be helpful when dealing with specific considerations e.g. engaging young people with cystic fibrosis who should not be in close contact because of cross-infections;
- Listening first – although not always possible, conducting a listening exercise with the young people to be engaged, to understand what they want to be engaged about, can strengthen engagement and provide useful ideas for routes and places of engagement;
- Language is important – how much information to engage with and how to present it, striking a balance between effective explanation but avoiding being patronising. Linguistic tools can be very effective (e.g. metaphors, similes) and benefit from having young people involved in developing these. Jargon and acronyms to be avoided at all costs!
- Who does the engagement? It can be useful for both researchers and non-researchers (e.g. public engagement professionals) to carry out engagement with research. Researchers provide ‘real-life’ examples but can sometimes represent authority with both positive and negative connotations; public engagement professionals can bring creativity and impartiality to the process;
- Parental input to engagement can be helpful (e.g. extending the engagement into the family home) though is not a pre-requisite for engagement.
- More could be done to engage young people from more diverse areas, backgrounds and personal circumstances;
- Effective engagement takes time, expertise and resource.

Active involvement of young people in research

Examples of young people's involvement in research are:

- as joint grant holders or co-applicants on a research project;
- involvement in identifying research priorities;
- as members of a project advisory or steering group;
- commenting and developing patient information leaflets or other research materials;
- undertaking interviews with research participants;
- user and/or carer researchers carrying out the research.

[INVOLVE](#) provides good resources on involving young people in research. The National Institute of Health Research (NIHR) has supported the establishment of Young Persons' Advisory Groups for research and the [GenerationR](#) – young people improving health through research – initiative.

Our experience of active involvement of young people in research suggests that:

- Awareness of what research is and how it is carried out often needs to be raised before effective involvement can happen – hence the need for engagement. For example, while many young people are aware of the concept of a clinical trial, fewer can clearly explain how and why controlled experimentation works ([Wellcome Monitor 2013](#));
- Conversely, some young people involved in research are already very expert in their condition and research into it. In situations where young people from both groups (i.e. research-naïve, research-expert) are involved in research, peer-to-peer learning can be really effective;
- The methods used to actively involve children in research will often be different from those used to involve adults in research – including considerations of place, audience and method (see above). Specific groups of young people will require extra flexibility in terms of methods to involve;
- Parental input to engagement can be helpful (see above) but can also be inhibiting in more active involvement situations. Perhaps because engagement and involvement are not overtly linked to research participation, parents are often (in our experience) happy to give autonomy to the young person who is being engaged and/or involved. In some situations, it has been interesting to garner both perspectives (adult and young person) on the same issues for involvement;
- Effective active involvement takes time, expertise and resource;
- More could be done to involve young people from more diverse areas, backgrounds and personal circumstances.

Ethics of engagement and involvement

There debate about the governance of engagement and involvement activities. Some engagement activities require ethics committee approval (e.g. activities that might involve vulnerable young people, activities that are being carried out in NHS locations/clinics) but guidance varies. Often, evaluation data gathered from engagement activities is subsequently used for diverse purposes. The use of people's 'stories' as tools for engagement has also raised ethical considerations.

Arguably, involvement of people, including young people, in research makes for more ethical research. However, the impact of active involvement (and engagement) of people in research is still under-researched and more effort is being devoted to this area in the UK.

What happens when the engagement is over? Effective engagement can raise thought-provoking social and health considerations amongst young people; active involvement can require considerable long-term investment (time and money). What do public engagement practitioners and researchers need to put in place to ensure socially responsible engagement and involvement?

Regulation of research with children in Malawi and challenges that arise when doing research with children

- *Neema Mtunthama Toto*

The National Commission on Science and Technology (NCST) regulates research in Malawi. NCST powers are delegated to the National Health Sciences Research Committee (NHSRC) and the College of Medicine Research and Ethics Committee (COMREC). The Committees review and approve health research in Malawi. NHSRC reviews proposals of national interest (e.g. vaccine trials, human genetic studies, stem cell research, cloning, national health surveys). COMREC reviews research from the College of Medicine, and its affiliates.

Both Committees have multidisciplinary membership to provide sufficient scientific and ethical review of research protocols. There is at least one lay member not affiliated to the two institutions. Review meetings are closed. Research proposals that will involve adults or children undergo similar review process.

NCST guidelines require that written informed consent is obtained from each research participant who is legally, mentally and physically able. For those that are not (including minors), permission is sought from parents or legal guardians or legally authorised representatives. Also, research staff need to get assent from minors who are capable of assenting while taking account of age, maturity, and psychological condition of children involved.

Clinical trials are required to provide trial insurance of no-fault.

Challenges experienced in clinical research involving children

Assent

- There are no guidelines for assent as to what needs to be in assent, the format, and depth of content. Researchers decide themselves how the assent should be. They also decide on the age range to apply the assent to. There are inconsistencies across research studies. Sometimes the ethics committees would instruct the researcher to include assent.
- Difficult to recruit 'parents' and their children to studies if the 'parents' are 16-18 years old. Researchers tend to exclude this age group for no clarity on who need to give consent.
- Research staff are not confident to obtain assent as they struggle to involve children. Children often fear hospitals and nurses. There are often difficulties to gain their trust as nurses are associated with pain. Most children and adults do not want to participate in studies involving blood collections.

Guardians/parents and children factors

- Lack of knowledge on research by guardians and children.
- Difficulties experienced by consenting research staff to explain research to guardians and children who do not know what research is.
- Guardians and children from low social economic background have difficulties to understand research or differentiate it from standard care.

- If child is very sick, some often accept to be in research with the hope that their child will get better care.
- If a child died while in research, parents decline children participation in new/future studies.
- Studies involving children with HIV where the HIV status has not been disclosed yet to a child, guardians and research staff have difficulties to explain to the child what the research is about. Often, the child is not actively involved in the studies. As children get older, they tend to refuse study participation.
- Some parents push their children (for the parent's interest) to participate in the studies that they do not want. The children end up not complying with the research procedures/regimes.

Health care providers factors

- It is not a common practice to involve parents and children in the children's care in hospital. Health care providers tend to focus more on the disease than the person (child and guardian interests are not dealt with). This causes difficulties to engage guardians and parents when it comes to research.

Study design factors

- Timing of consent is not always ideal for the guardian. Sometimes there is no allowance to allow female guardians to get consent from their spouses. This causes difficulties to enrol and retain paediatric participants.
- Language translation difficulties especially in genetic studies and others where there are no words in local languages. Consenting staff struggle to explain to guardians and children. Guardians also find it difficult to understand and participate in such studies.
- No direct/immediate 'benefit' or results to guardians / children – some studies e.g. genetic ones do not give results to the guardians. As such, guardians do not perceive the studies as beneficial to them or their child's participation. Research staff struggle to get participants to such studies.

Doing paediatric clinical trials in Peru and in the Latin America region: current challenges

- *Claudio F. Lanata, MD, MPH*

Peru has had a large experience conducting clinical studies and clinical trials in paediatrics for many years. The Nutrition Research Institute (IIN) in Lima, started doing such studies in the 1960s, and established the first ERB registered in the US in the country. Clinical trials, mostly phase II and III, have been done from few hundred participants to a cholera vaccine trial with 92,000 subjects vaccinated in one month, which included children 5-17 years of age. The largest trial done recently has been the phase III efficacy vaccine trial of the GSK oral rotavirus vaccine where the IIN enrolled 12,000 infants of two months of age in a five-month period, being the largest enroller of the 66,000 infant trial size. This has produced a large and important experience how to conduct such trials, having very positive reviews and audits from sponsors and FDA and EMA inspections. These trials have facilitated the rapid introduction of these vaccines into the country when they became available.

For many years, conducting clinical trials in Peru only needed approval of the sponsor, the research institution and the local ERB. For some studies, researchers asked for the Peruvian Ministry of Health (MoH) endorsement, which was directly requested to the Minister or high level officials. In 2003 the MoH appointed the Peruvian National Institute of Health (INS) to be in charge of approving clinical trials in Peru, through the General Office of Research and Technology Transfer (OGITT). To comply with this request, a committee within OGITT elaborated the first Clinical Trial Bylaws for Peru, which was officially approved in July 2006, at the last day in office of the government of that time, without any public hearing. When the new government took power and the new Minister of Health took his office, it was realised that the approved bylaws could not be complied with, because many requirements were not feasible in Peru (like malpractice health insurance, not available still in Peru). The MoH created a committee to review the bylaws and, after public consultation and participation from main bodies in the country (Peruvian College of Physicians, MoH officials, Universities and main research centres), a modified Bylaw was approved in 2007, which is still in force. These bylaws introduced the following requirements, which have generated the following issues in conducting clinical trials in general, and with children in particular:

- The signature of both legal parents in the informed consent form for children participation. This has created major logistical problems since fathers, who usually are absent for work, can't attend study clinics for the enrolment process, making those families unable to join studies. This is also a problem when the biological father no longer lives with the child's mother. In the current bylaws, it mentions that one biological parent could be excused to sign the informed consent form when they are impeded to attend the enrolment session. OGITT has interpreted this clause in a legalistic way: the other parent needs to show a valid certificate of a deceased parent, or being in jail. No other excuses are accepted. Finally, OGITT has asked investigators to photocopy the parents' National Identity Cards, to check the names, date of birth, and most importantly, their signatures, to assure that it matches those in the informed consent form. About 20% of Peruvians have lost them or they have not renewed their cards,

again making them unable to join studies until a valid ID is shown. Comparing the number of children with the correct age to join a study identified in a house-to-house census of a potential study area with those who enter into a study, we have seen that about a third of those potentially eligible participate in the enrolment process, creating an important selection bias.

- In Peru individuals 18 years of age and older are considered adults. OGITT has requested that any parent under that age can't consent for their child to enter into a clinical trial without the co-signature of one of his or her parents (the child's grandfather or grandmother), even though the MoH provide rights to any parent, regardless of their age, to make decisions about their children. Peru has about 20% of pregnancies in adolescent girls. This rule creates another obstacle to allow children from under-age parents to enter into clinical trials.
- To have an insurance policy, with legal representation in Peru, for compensation for possible damage due to the study product. Such insurance policies are not available in Peru, they need to be purchased outside the country. This favours big pharmaceutical companies and creates difficulties for non-commercial sponsors, like the US NIH.
- Most families interpret the existence of the compensation policies as a general health insurance, and demand for free care and free medications from the study when not provided by the MoH system. This has been solved by many investigators, by adding a budget line in the study to cover for those needs, which is not always accepted by sponsors.

From the beginning, however, some have seen the 2007 modifications of the Peru Clinical Trials Bylaws as a "set back", relaxing Peru requirements, and have campaigned for much tighter regulations. Following an effective media campaign, a Supreme Decree signed by the President of Peru was issued in June 2015 ordering to stop approvals of any paediatric clinical trials in the country, until a new Clinical Trial Bylaws was approved. It also orders the INS to inspect all ongoing paediatric clinical trials. Such inspections were done, and unofficially they have not found any major problem with current and recent trials done with children in Peru. A proposal for a new Clinical Trial Bylaws was published for public opinion by the MoH, which again generated a lot of negative comments to some clauses, like "providing any study product with a positive result to all study participants for life or until they can purchase it on their own". The MoH has decided not to act, and the banning to do paediatric clinical trials continues. It seems that this situation will need to be solved by the new government, scheduled to take office on 28 July 2016. The number of clinical trials conducted in Peru has been drastically reduced, even in adults.

Similar challenges to the acceptability of clinical trials have been experienced in a number of other countries in Latin America, including Brazil, Costa Rica and Chile.

Overview of the regulatory framework for biomedical research involving legal minors in Singapore

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Member, Ethics Review Board, Médecins Sans Frontières

In Singapore, a person under 21 years of age (called a 'legal minor') does not usually have the legal capacity to make significant decisions concerning his or her custody, care and control, unless otherwise empowered by law. Such decisions will be made on this person's behalf by his or her parents or legal guardian. Under the *Children and Young Persons Act*, the welfare and best interests of a person below 16 years of age is to be the first and paramount consideration in all decisions made on his or her behalf.¹² While there is no explicit provision for a legal minor above 16 years of age, the 'best interests' standard in decision-making is generally regarded as applicable under the common law. As a general legal position, a legal minor between the ages of 16 and 21 years is not regarded as having sufficient capability (or maturity) to independently decide on whether to participate in biomedical research that carries significant risk. This capability or maturity is itself a matter of judgment, as it is to be assessed based on a number of considerations include the person's age, ability, experience, education, exhibited judgement, conduct, general appreciation of relevant risks and consequences, psychological state and marital status.

Clinical trials regime

Where clinical trials are concerned, the Medicines (Clinical Trials) Regulations (MCTR) requires only the consent of the legal minor if he or she is married. However, if the legal minor is not married, then both his or her consent, as well as that of his or her parent, guardian or legal representative (deciding on a 'best interests' basis) must be obtained. The legal minor's consent shall not be required if he or she lacks sufficient understanding to provide such consent, and there is a reasonable prospect that participation in the clinical trial will directly benefit him or her. Direct benefit to the subject is predicated on appropriate animal and other pre-clinical studies having been conducted, and the information derived from those studies and related evidence must support the potential for the proposed use of the test material to provide a direct benefit to the research participant. Risks associated with the clinical trial must also be reasonable in relation to what is known about the medical condition of the subject, the risks and benefits of standard therapy (if any), and what is known about the risks and benefits of the proposed use of the test material. In addition, the clinical trial must be of a nature that it cannot be practically carried out using only subjects who can give their own consent.

Human biomedical research regime

More recently, Singapore's Parliament enacted the Human Biomedical Research Act (HBRA) on 18 August 2015, which establishes a relatively comprehensive legal framework on research involving human participants (other than clinical trials) and

¹² Section 3A, Children and Young Persons Act, Chapter 38 of Singapore.

their biological materials. This legislation essentially builds on a system of ethical governance that has been instituted by the government, on the advice and recommendations of its Bioethics Advisory Committee (BAC). Where the conduct of human tissue banking and biomedical research using human tissue (including those from legal minors) in Singapore are concerned, a set of ethical guidelines has been published by the BAC in its report on 'Human Tissue Research' in November 2002.¹³ These guidelines have regulatory effect on all locally registered medical practitioners and publicly funded research.¹⁴ The ethical principles embodied in the guidelines include the primacy of the welfare of tissue donors, the need for informed consent and confidentiality, respect for the human body and sensitivity towards the religious and cultural perspectives and traditions of tissue donors. These principles have been applied by the BAC in a set of more detailed guidance on biobanking and research involving human biological materials.¹⁵ A number of the ethical provisions are now also legal requirements, set out within one of the two governance regimes (on tissue banking and on human biomedical research) that make up the HBRA. In addition, operational requirements are necessitated as specific legal duties of a regulated person or entity. These include the submission of a declaration of compliance with prescribed statutory and regulatory requirements, designation of a person who will be held accountable, and the formulation and implementation of appropriate standards, policies and procedures.

Tissue Banking. The legal requirements of the HBRA are applicable to any individual, body of persons (whether corporate or unincorporated) or organisation that carries on or conducts any tissue banking activity, legislatively defined as "a structured and an organised activity involving human tissue for the purposes of facilitating current or future research or for public health or epidemiological purposes or any combination of such purposes including...(a) the collection, storage, procurement or importation of human tissue; [and] (b) the supply, provision or export of human tissue".¹⁶ The BAC's firm stance against the commercialisation of the human body (or any part thereof) is enshrined in the rule prohibiting the sale or supply of any human tissue for valuable consideration, as well as any advertisement to that effect.¹⁷ The ethical requirement of informed consent is also a legal requirement, and support by a further rule against compelling or deceiving a person to donate tissue.¹⁸ Where the prospective tissue donor is a legal minor (i.e. a person less than 21 years of age), the presence of therapeutic purpose may be required in addition to the consent requirement:¹⁹

- (a) Where the minor has sufficient understanding and intelligence to enable the minor to understand what is proposed in the procedure, consent is to be obtained from both the minor and at least one adult parent or guardian of the minor;

¹³ Bioethics Advisory Committee. *Human Tissue Research*. Singapore: Bioethics Advisory Committee, November 2002.

¹⁴ Ministry of Health. Directive 1A/2006: BAC Recommendations for Biomedical Research, 18 January 2006.

¹⁵ Bioethics Advisory Committee. *Ethics Guidelines for Human Biomedical Research*. Singapore: Bioethics Advisory Committee, June 2015, Part V, pp.41-48.

¹⁶ Human Biomedical Research Bill, Bill No. 25/2015 of Singapore, Section 2.

¹⁷ *Ibid*, Sections 32 and 33.

¹⁸ *Ibid*, Sections 37(1) and 38.

¹⁹ *Ibid*, Section 10(1).

- (b) Where the minor does not have sufficient understanding and intelligence, consent must be obtained from at least one adult parent or guardian of the minor, and provided that the removal of the tissue is primarily for a therapeutic or diagnostic purpose; and
- (c) Where the minor lacks mental capacity, the removal of tissue must similarly be primarily for a therapeutic or diagnostic purpose, and consent must be obtained from a duly authorised deputy or from at least one adult parent or guardian of the minor.

However, the requirement that the removal of the tissue is primarily for a therapeutic or diagnostic purpose may be waived by an IRB if the removal of the tissue involves no more than minimal risk to that person, and there are reasonable grounds for believing that the proposed areas of research cannot be carried out without the use of the tissue from the class of persons to which that person belongs.²⁰

Human Biomedical Research. For human biomedical research involving legal minors other than in clinical trials or tissue banking, the legislative requirements are broadly similar to those that apply to tissue banking.²¹ Where the minor has sufficient understanding and intelligence as to what is proposed in the biomedical research, consent is to be obtained from both the minor and at least one adult parent or guardian of the minor. Whereas consent from the adult parent or guardian may be waived by the IRB in specified circumstances, consent from the minor must still be obtained. Should the minor lack the requisite understanding and intelligence, or mental capacity, there must be reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of minors to which the minor belong, in addition to obtaining consent from at least one adult parent or guardian (or authorised deputy, where the minor lacks mental capacity).

While the HBRA represents a crucial policy milestone for biomedical research governance in Singapore, its requirement of ‘dual consent’ (i.e. from the legal minor and from a parent or legal guardian) is not substantively different from major scientific jurisdictions. The HBRA also does not render the underlying ethical governance otiose, particularly where judgment is required as to appropriate risk-benefit ratio, for instance.

‘Dual consent’ requirement

The capability of young children to participate in decisions about both medical treatment and research are increasingly recognised in North America and Europe, and the importance of obtaining the ‘assent’ or acquiescence of the child before proceeding with research is widely emphasised in professional guidance. In the US, the assent of a child is generally described as an ‘affirmative agreement’ that should be obtained. While it is not comparable to the informed consent of a competent adult, a research may only proceed if the child’s assent is accompanied by consent from a parent or a legally authorised representative. In practice, assent could be regarded as a mechanism for engaging the child in the research process, in such a way as to respect the child’s views and preferences, and to provide the child with as

²⁰ *Ibid*, Section 10(3) and Section 37(3).

²¹ *Ibid*, Section 8.

reasonable an explanation as possible, consistent with the child's level of understanding and mental capacity. While the EU Directive does not use the term 'assent', it specifies that the parent's consent "must represent the minor's presumed will",²² and the EU *ad hoc* group guidance on the Directive emphasises that investigators should actively seek assent from child participants. The *ad hoc* group guidance suggests that children as young as three may have "the emergent capacity to agree", and that from this age up some form of assent should ordinarily be sought.²³ In order for such assent to be meaningful, information about the trial, tailored to the needs and abilities of the child, clearly needs to be available. The requirement that such information is provided by specialist staff emphasises the important role potentially played by doctors and researchers, as well as parents, in maximising a child's ability to participate meaningfully in the decision-making process.

While emphasis on the importance of involving children in decisions is very much in line with current good practice and professional guidance, difficulties arise in two circumstances: where a child wishes to participate in research *without* the consent of his or her parents (this may arise for example in research related to sexual health), and where a child does not wish to participate, despite his or her parents' consent. The approach taken in the EU Directive that a minor's wish to refuse should only be "considered" differs from standard professional practice and international conventions. The EU *ad hoc* group, for example, states that if a minor wished to withdraw from a trial, "the child's will should be respected". The CIOMS guidance similarly states that "a child's refusal to participate or continue in the research will be respected".²⁴ Regulations in the US allow the requirement of assent of the child to be waived if the child is incapable of providing this, or if the research holds a prospect of direct benefit to the child's health or wellbeing and available only in the context of the research.²⁵

Ultimately, the difference between 'assent' and 'consent' may not be so important if 'consent-taking' is properly implemented as a holistic and substantively meaningful engagement between researchers and legal minors, together with their caregivers. Recent empirical research suggests that, in practice, most researchers in fact operate a 'family decision-making model' where researchers and clinicians work with the whole family to maximise understanding and come to an agreed decision. Paediatric research also suggests that most children want their parents or legal guardians involved in research decisions. A parent's rights in connection with their child are not absolute, and are subject to the 'welfare principle'. Where participation in biomedical research is concerned, parents are still required to meet the conventional legal requirement to act in their child's best interests. This requirement

²² Article 4, Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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.

²³ See Section 7.1, Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population, Recommendations of the *ad hoc* group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, 2008.

²⁴ Guideline 14, International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: Council for International Organization of Medical Sciences, 2002.

²⁵ 45 CFR 56 Subpart D, §46.405.

may be difficult to satisfy when it is unclear how directly a legal minor will benefit from research participation, or when the risk-benefit ratio cannot be clearly ascertained.

Ambiguities in benefits and risks

In some cases, particularly where a child is seriously ill and no other treatments are available, parents may consent to their child being enrolled in a clinical trial of a new medicine purely based on the hope that the medicine may turn out to benefit their child. In other cases, any possible benefit to the child will be much less direct, such as where healthy children are involved in vaccine trials. In addition, clinical trials may often involve additional procedures, such as blood tests or scans, undertaken with the aim of generating additional research data. It is not entirely clear in what sense such procedures can be said to be in the child's 'best interests'. In addition, it is also unclear how 'direct' the benefit must be. Where legal or regulatory requirements include 'direct' benefit to be obtained for the group of children participating in the trial (such as those under the MCTR), this suggests that incidental or 'collateral' benefits (such as additional monitoring and health checks) may not amount to a child's best interests. Regulatory clarification in this regard will be helpful.

In the US, regulations governing paediatric research interventions distinguish between research interventions that offer a 'prospect of direct benefit' to the child participant, and those that do not. Where no prospect of direct benefit exists, research may only go ahead if it poses 'minimal risk' or risks that are no greater than a 'minor increase over minimal'. Where research offers prospect of direct benefit, then the US Regulations permit risks that are "justified by the anticipated benefits to the subjects",²⁶ thus potentially allowing for higher risks (for example, of as yet unknown side-effects) where the potential for benefit for the subject is also thought to be high and adequate provisions are in place for soliciting the child's assent and parents/guardians' permission. However, the EU Directive on good clinical practice in the conduct of clinical trials distinguishes much less clearly between research that may offer prospect of direct benefit to participants, and that which does not. The EU Directive permits only research that will obtain "some direct benefit for the group of patients".²⁷ While the Directive itself does not define specifically what is meant by the 'group' of minor patients concerned, the EU Commission's *ad hoc* group defines 'group' as "children affected by the same disease, or a disease which shares similar features and for which the medicinal product could be of benefit".²⁸ The Directive allows for research that is unlikely to generate direct benefit, so long as it could benefit other children with the same or similar condition. However, in contrast to the Declaration of Helsinki and the Oviedo Convention, the EU Directive does not specify a threshold of permitted risk. Instead, it requires the trial to be designed to "minimise pain, discomfort, fear and any other foreseeable risk" and for the risk

²⁶ *Ibid.*

²⁷ Article 4, Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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.

²⁸ See Section 12, Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population, Recommendations of the *ad hoc* group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, 2008.

threshold and the degree of distress to be defined and constantly monitored. It also does not distinguish between risks to trial participants who may themselves benefit from the research from those who do not.

Where clinical trials are concerned, the MCTR in Singapore requires some direct benefit to be obtained from participation in a clinical trial. Where the subject is a legal minor or a person who is unconscious or incapable of exercising rational judgement, there should be a reasonable prospect that participation in the clinical trial will directly benefit that subject. Singapore's position differs from most regulatory systems, international statements and professional guidelines, which allow for the possibility of legal minors incurring some degree of risk without benefit to themselves in the research context. As noted above, many limit such risks either to 'minimal' or to a 'minor increase over minimal', while the EU Directive makes reference simply to 'minimising' risks. The recommendations of the EU *ad hoc* group suggest that 'minor increase over minimal risk' is acceptable where there is benefit either to the individual or to the group, and where the benefit-to-risk balance is at least as favourable as that of available alternative approaches. 'Greater than minor increase over minimal risk' is only permitted where there is benefit for the individual concerned, and that benefit is especially favourable in relation to available alternative approaches for the individual's condition.²⁹

As mentioned, the US regulations permit 'minor increase over minimal risk' where the research does not offer participants the prospect of direct benefit but where "the intervention or procedure is likely to yield generalisable knowledge about the subjects' disorder or condition, which is of vital importance for the understanding or amelioration of the subjects' disorder or condition".³⁰ This approach has been criticised on the basis that it may potentially allow greater 'net risk' (i.e. risk that is not justified by the possible benefits) in circumstances where the research does not offer prospect of direct benefit. In contrast to the current US approach, the EU *ad hoc* group guidance does not distinguish between benefit to the individual and benefit to the wider group. This approach has equally been criticised for the difficulty in assessing the risk-to-benefit ratio at a group-level as opposed to individuals. In Singapore, how risk and benefit thresholds are to be determined and assessed to be acceptable require further regulatory attention and clarification.

²⁹ *Ibid*, at Section 12.1.

³⁰ 45 CFR 56 Subpart D, §46.406 and §46.407.