British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **81** 857–864 857

CLINICAL TRIALS

The potential exploitation of research participants in high income countries who lack access to health care

Correspondence Dr R Dal-Ré, Investigación Clínica, Programa BUC (Biociencias UAM + CSIC), Campus de Excelencia Internacional, Universidad Autónoma de Madrid, Ciudad Universitaria de Cantoblanco, c/Einstein 3, E-28 049 Madrid, Spain. E-mail: rafael.dalre@fuam.uam.es

Received 2 September 2015; **revised** 25 December 2015; **accepted** 3 January 2016

Rafael Dal-Ré[1], Annette Rid[2], Ezekiel Emanuel[3] and David Wendler[4]

[1]Clinical Research, BUC (Biosciences UAM + CSIC) Program, International Campus of Excellence, Universidad Autónoma de Madrid, Madrid Spain, [2]Department of Social Science, Health and Medicine, King's College, London, UK, [3]Department of Medical Ethics and Health Policy, University of Pennsylvania, Philadelphia, Pennsylvania, USA and [4]Department of Bioethics, NIH Clinical Center, Bethesda, Maryland, USA

Keywords clinical trials regulation, drug development, ethical trial conduct, exploitation of participants, fair benefits framework, poor trial participants

There are millions of individuals living in North America and the European Union who lack access to healthcare services. When these individuals participate in research, they are at increased risk of being exposed to the risks and burdens of clinical trials without realizing the benefits that result from them. The mechanisms that have been proposed to ensure that research participants in low- and middle-income countries are not exploited are unlikely to protect participants in high-income countries. The present manuscript argues that one way to address concerns about exploitation in high-income countries would be to require sponsors to provide targeted benefits such as medical treatment during the trial, or the study drug after the trial. The latter could be achieved through extension studies, expanded access programs, or named-patient programs. Sponsors also might provide non-medical benefits, such as education or social support. Ethical and regulatory guidance should be revised to ensure that research participants in high-income countries who lack access to healthcare services receive sufficient benefits.

To protect participants from exploitation, the risks and benefits of research need to be distributed fairly [1] (Box 1). To date, proposals to address this concern have focused on clinical research conducted in low- and middle-income countries (LMICs) by sponsors from high-income countries (HICs) [1–5]. This focus is based on the assumption that the potential to exploit research participants is not a significant concern in HICs. Wealthier countries have reliable mechanisms to approve tested products and make them available to those who need them. These mechanisms decrease the potential for exploitation by providing study participants with access to the beneficial products developed through clinical research.

Box 1

Two conceptions of exploitation in clinical research

The Kantian conception of exploitation (treating individuals as a means only and not as an end in themselves) primarily translates into the use of individuals in clinical trials, without their consent. For present purposes, we are assuming that all trial participants provide consent. Thus, this first conception of exploitation is not relevant to the concerns raised in the present article.

DOI:10.1111/bcp.12879

A second conceptionof exploitation, elaborated by Alan Wertheimer, understands the potential for exploitation in terms of sponsors (and others) taking *unfair advantage* of research participants [6]. Exploitation in this sense is transaction specific and concerns the outcome of individual transactions. This account allows for the possibility that an individual may be exploited even though she consents to the transaction and benefits from it. Vulnerability, on this view, is neither necessary nor sufficient for exploitation.

Reliance on approval and distribution of interventions found to be effective helps to address the potential for exploitation as long as research participants have access to healthcare services. Unfortunately, there are now tens of millions of poor individuals living in North America and the European Union (EU) who have limited or no access to healthcare services. When these individuals participate in clinical trials, they are at increased risk of being exploited. Specifically, there is an increased chance that they will face the risks and burdens of research participation while the benefits accrue to others. The present paper calls attention to this neglected concern and describes a possible way to address it.

Access to health care in North America and the European Union

In 2012, approximately 48 million individuals living in the US did not have health insurance [7]. Several million have gained insurance through the Affordable Care Act [8], suggesting that the number of individuals currently living without health insurance in the US is likely to be between 30 and 34 million [9]. A small number of these individuals have the financial resources to pay for medical care out of pocket. The vast majority are poor and have access to only limited medical care through hospital emergency departments. In addition, there are 5–6 million undocumented migrants in the US who have even lower access to healthcare services [9] and some 12% of chronically ill adults reported having stopped taking their prescribed medications for cost-related reasons [10].

Canada provides universal access to medical and hospital care, but not to prescription drugs. Medicines are provided through fragmented public and private drug plans, leaving many Canadians with little or no access to needed medicines [11]. Indeed, 10% of Canadians cannot afford to take their medications as prescribed [12]. In addition, some 500 000 non-status migrants are not eligible for Provincial health coverage [13], although these individuals may be able to access free care at community centres run by volunteer-run inter-professional teams of primary care professionals [14].

Millions of individuals in the EU, especially in Southern Europe, have decreasing or no access to healthcare services [15]. For example, an estimated 800 000 Greek citizens currently do not have healthcare coverage [16]. In addition, several countries have introduced or increased user charges or co-payments for selected services (e.g. prescription medicines). These fees pose a particular challenge for individuals with low incomes [15, 17].

There are another 2–4 million irregular migrants in the EU [17]. A 2008 report by Médecins du Monde, a non-governmental organization providing medical care and other support to vulnerable populations, found that health care is not guaranteed for irregular migrants, even in countries where healthcare costs are supposed to be covered for all patients [18] – thereby failing to fulfil their right to health [19, 20]. This situation has worsened recently, as shown in Table 1. In 2012, more than 80% of patients visiting Médecins du Monde clinics in seven Western European countries had no access to health care without paying the full cost [21]. Similarly, in the UK, 618 000 undocumented migrants

Table 1

Health and social key figures regarding 8412 patients attended at Médecins du Monde clinics in seven European countries, 2012 [21]

1. Health data	
No. of medical consultations	10 968
No. of diagnoses	11 921
Diagnoses requiring essential treatment	76%
Most frequent chronic diseases/conditions	
Hypertension	7.80%
Diabetes	4.75%
Other (relevant) chronic diseases/conditions	
Cancer	0.36%
HIV	0.23%
Chronic diseases of all diagnoses	61%
Patients needing essential treatment that had not received any when being attended at Médecins du Monde clinics	>50%
Patients reporting having been denied access to care by a healthcare provider in the last 12 months	20%
Patients having given up seeking health care in the last 12 months	36%
No health coverage at all, fully chargeable	81%
2. Social data	
Most common regions of origin by country	
Belgium: Magreb	38%
France: Magreb	36%
Germany: European Union	55%
Greece: Greece	49%
Spain: Americas	45%
The Netherlands: Sub Saharan Africa	61%
UK: Asia	56%
Not permitted to reside in the host country	61%
European Union citizens not permitted to reside in the host country	55%
Undocumented migrants from a non-European Union Member State	50%
Unstable or temporary housing	49%
Have a job or activity to earn a living	25%
Patients needing an interpreter	40%

lack access to health care, with the exception of emergency services [22]. While these developments have been influenced by the financial crisis and resulting austerity measures, as well as international conflicts, there unfortunately is little reason to think they will be fully reversed in the near future.

There have been several efforts in HICs to reduce the number of individuals who lack health insurance [23, 24] and to provide health services to all individuals [25]. A recent analysis found that providing universal public access to prescription medicines in Canada would not be prohibitively expensive [26]. Moreover, a number of groups advocate increased access to health care for poor populations [27, 28]. Once included within the healthcare system, trial participants would gain access to the interventions that are developed through clinical trials or to commercially available interventions approved for their disease or condition. However, until full access is realized, millions of individuals who live in HICs are at risk of being exploited, facing the risks and burdens of participation in clinical trials without having access to the beneficial interventions that result from the trials.

Proposals to address exploitation in low- and middle-income countries

The potential to exploit research participants has been widely discussed with respect to research in LMICs. In particular, it is recognized that individuals and host communities in LMICs may face the risks and burdens of clinical trials while the benefits go to those living in HICs [29]. One of the first attempts to address this concern has come to be known as the 'reasonable availability' requirement. This requirement mandates that products shown to be effective during a trial should be made reasonably available to the participants and host community [2, 4]. While this approach provides a way to address the potential for exploitation in some trials, most trials with investigational medicines do not identify a safe and effective intervention [30]. As a result, the reasonable availability requirement fails to ensure sufficient benefits for the participants of many clinical trials [5].

With this in mind, a number of alternatives to the reasonable availability requirement have been proposed. The 'fair benefits' framework specifies that research participants and host communities should receive a fair level of benefits, given the risks and burdens to which they are exposed, and the extent to which others benefit from their participation [31]. This approach prohibits sponsors from providing research participants with insufficient benefits, even when participants agree to them during the informed consent process [32].

The fair benefits framework can be effective in settings where research places burdens on host communities, and participants benefit from measures that are provided to the larger community (Box 2). However, burdens to the host community typically are not a concern for research in HICs. In addition, people who are poor and lack access to health care often represent only a minority of those who live in a given jurisdiction in HICs. As a result, providing benefits to the host town or city [4, 5] may not address the potential exploitation of research participants in HICs. Moreover, the types of benefit offered in LMICs, such as development of healthcare infrastructure, typically already exist in HICs. The problem is that poor individuals often do not have access to the infrastructure that exists in their communities.

Box 2

Prevention of exploitation of research participants in lower- and middle-income countries (LMICs)

Two main approaches have been described, the reasonable availability requirement and the fair benefits framework.

a) Reasonable availability requirement.

This approach specifies that trial participants and, when appropriate, host communities should be ensured reasonable access (e.g. the ability to purchase at a fair price) interventions that are proven efficacious by the trials in which they are involved. Providing interventions to participants after a trial has completed (i.e. post-trial access) is one way to ensure reasonable availability. This approach has been implemented in many HIV trials, although generally for a specified period of time only. For example, 13 out of 18 NIH-funded HIV antiretroviral therapy trials conducted during 2005–2007 in LMICs included post-trial access for trial participants, although long-term access to antiretroviral therapy was not guaranteed [33]. A different approach was adopted in nine HIV prevention trials: access to antiretroviral therapy for participants who seroconvert during the trial [34]

b) Fair benefits framework.

This approach specifies that research participants and communities should receive a fair level of benefits. This might include reasonable availability of the study intervention or other benefits. Common examples for participants are medical benefits, such as free treatment for infections, prompt and timely treatment of acute illnesses and referral of chronic cases to government facilities; benefits for communities could include lab and clinical equipment support and health staff training, training of home-based caregivers, sustainable prevention education through peer educator programmes, delivery of preventive interventions or emergency response to natural disasters [35–37]. Non-medical benefits might include transportation to hospital for treatment, food tickets for very poor individuals, employment opportunities, donation of used study vehicles or refurbishment of facilities [34, 35].

NIH: US National Institutes of Health.

HIV: human immunodeficiency virus.

Addressing exploitation in high-income countries

Regulations and guidelines in HICs attempt to address a number of ethical concerns raised by research with poor individuals, including fair subject selection and informed consent [1]. And independent review committees – such as research ethics boards in Canada, research ethics committees in the EU and institutional review boards in the US – are in place to ensure that individual trials satisfy these requirements.

In contrast, existing regulations and practices in HICs are based on the assumption that research participants ultimately have access to products developed through clinical trials. As a

result, the potential exploitation of individuals who lack access to healthcare services has gone unaddressed [38]. To remedy this gap, national and international guidelines and regulations should be revised to recognize and address the potential exploitation of individuals living in HICs. One possibility would be to specify that sponsors should provide individually targeted benefits to poor individuals in HICs who lack access to healthcare services. Provision of healthcare services would offer important benefits. And sponsors and investigators typically have the capacity and expertise to provide them. For example, sponsors could provide additional ancillary care beyond what is owed to all participants during the trial [39]. Alternatively, sponsors could provide post-trial access through a follow-up extension study. This approach might be particularly beneficial to individuals who have chronic diseases or conditions. Sponsors and independent review committees should be vigilant to ensure that proposed benefits reach their intended beneficiaries, especially with respect to the trials conducted by third parties (e.g., contract research organizations) or private-sector physicians who participate mainly for financial reasons [40].

Another option would be to provide benefits through specific programmes (Box 3). When reliance on a follow-up extension study is not feasible, expanded access programmes might provide the experimental drug to participants who lack access to medical care after the trial. This approach would require regulatory changes to permit patients who suffer from chronic diseases or conditions to benefit, not only those that are life-threatening or seriously disabling and with unavailable treatment [41–43]. Once an investigational drug has been marketed, an expanded access programme should be considered, both as a way to benefit participants and to gather long-term safety data.

Another approach would be to provide the new marketed drug at a subsidized price through non-governmental organizations. For trials that enrol only a few individuals who lack access to health care, these might involve 'post-licensed' named-patient basis programmes supported by the trial sponsor (Box 3). Independent review committees might decide that, once the

Box 3

Factors relevant to research with participants who are poor and lack healthcare coverage

1 Trial participation

1a) *Type of disease or condition.*
Individuals with chronic conditions have on-going healthcare needs. Many of these patients can participate in the same trials as the general population (e.g., post myocardial infarction, hypertension, diabetes).

1b) Lack of access
Except in specific diseases or conditions (e.g. HIV or emergency situation), the access of investigators to people that have no access to health care is very difficult. Even if accessible, patients should comply with the trial's selection criteria – an additional hurdle for them to be recruited. Generally speaking, a limited number of participants coming from this poor population should be expected.

1c) Type of trial

1c.1) Outcomes in phase 2 and 3 trials are uncertain and many participants will receive a placebo [44]. Therapeutic benefit is expected in phase 4 trials as all participants will receive approved medications for the indication of interest.

1c.2) Follow-up extension studies are rarely offered and available only for trial participants who meet the selection criteria. Usually all patients receive the same dose of the experimental medicine to gather long-term data. Depending on the indication, sometimes patients that participated in a phase 3 trial could be on treatment until the medicine is commercially available. A search on ClinicalTrials.gov identified only 140 extension studies conducted after phase 2 or 3 trials registered as of 28 November 2013. Of these, only some 58 had a follow-up period of at least 1.5 years – the minimum time considered necessary to have the medicine marketed after phase 3 trials are successfully concluded: half a year for marketing application submission to regulatory agencies and 1 year for its review [45].

For HIV, there were only four extension studies. One conducted in HICs and LMICs, another one in eight LMICs and the other two in the US. Furthermore, there was not a single 'open' extension study registered in this indication (Supplemental information).

1d) Care ensured while participating in the trial
The ancillary care model [39] offers an opportunity for participants to receive some benefits during the trial (see text).

2. Post-trial access to medication
Compassionate use, expanded access programmes or special access programmes offer access to experimental medicines for patients with life-threatening, long-lasting or seriously disabling illnesses who cannot be satisfactorily treated with commercially available medicines or included in clinical trials [41–43, 46]. In programmes involving a number of patients under a common protocol, the regulatory agency, the patients' physicians and the manufacturer are involved in the process. As of 28 November 2013, there were 80 available expanded access programmes registered on ClinicalTrials.gov. Three of these trials on HIV infection provide antiretroviral therapy for 1.2, 9.7 and 10.3 years. The three were running in HICs. There were very few compassionate use programmes (supplemental information).
A named-patient basis programme could be a practical solution when very few patients who are poor and lack access to health care are enrolled in a trial. In named-patient programmes, the physician requests the medicine directly to the manufacturer, with or without regulatory agency involvement [42, 43, 46]. A similar programme could be maintained after the new drug is marketed: a 'post-licensed' named-patient basis programme, in which poor former trial participants with no access to health care could be treated with the medicine. The long-term commitment of the trial sponsor/manufacturer is the critical factor in this type of programme.
Cost of the proposal: Take, for example, HIV infections and expanded access programmes lasting for 10 years (see above). In the European Union, relatively few patients will be recruited into trials due to two main factors: (a) lack of access to hospitals and clinics where trials are

conducted, and (b) failure to meet selection criteria. An expanded access programme for 100 patients lasting 10 years is more expensive than a named-patient programme for 10 patients lasting even 50 years.

HICs: high-income countries.

LMICs: low- and middle-income countries.

trial is over, alternative medications within the standard of care of the country would offer appropriate benefits. Whichever approach is adopted, regulators and healthcare providers should help to ensure that trial participants who lack adequate access to health care receive sufficient benefits.

In some cases, research participants who are poor and lack access to health care may benefit more from non-health-related benefits, such as education and training, or social services. In cases where the participants belong to a defined community, community programmes, such as health promotion efforts, could be implemented through health workers or non-governmental organizations [17]. Ideally, the proposed approach should be discussed with participant group representatives in advance, reviewed and approved by an independent review committee, and described in the protocol and informed consent documents [47].

Currently, there are no reliable estimates for how many poor individuals who lack access to healthcare services participate in clinical trials in HICs. Because this information is not disclosed in articles or in registries, the extent of the present concern is largely hidden from public view. One might thus argue that before we try to address the potential for exploitation, we should first determine the extent of the problem. Such efforts are important. At the same time, the present proposal is based on the assumption that we should not wait until we know exactly how many research participants are at risk of being exploited before we take steps to protect them. Sponsors should provide sufficient benefits to the poor individuals they enrol in research conducted in HICs, no matter what the total number of trial participants who lack access to health care might be across all trials in HICs.

Objections and replies

Some may object that offering benefits to poor individuals who lack access to healthcare services, such as a follow-up extension study, might unduly induce them to enrol in research [48]. Undue inducement occurs when the benefits offered to potential research participants are so large that they lead individuals to enrol in trials that are clearly contrary to their interests [49, 50]. Recognizing this, the most effective response to concerns regarding undue inducement is to ensure that the level of additional benefits offered to participants is commensurate with the risks and burdens posed by the trial. Thus, to address concerns about undue inducement without raising the potential for exploitation, independent review committees should ensure that the potential benefits to participants justify the risks they face or that any net risks (i.e. research risks that are not offset by potential clinical benefits) are not excessive [49, 50]. Importantly, independent review committees should not attempt to address concerns regarding undue inducement by eliminating potential benefits to participants because doing so only increases the potential for exploitation.

Still others may worry that the provision of targeted benefits will impose excessive costs on sponsors. First, we believe that it is important to address the potential for exploitation of research participants, even if it is expensive. Second, under the fair benefits framework, sponsors are obligated to provide benefits to participants as a function of the benefits that the sponsor derives from the participants' involvement in the study. Hence, sponsors are never obligated to provide more benefits to participants than the sponsor derives from the participants' involvement. Third, examples of expanded access programmes lasting some 10 years (Box 3) suggest that it can be feasible for sponsors to provide additional benefits to participants, especially as the expenses will likely be small in relation to the costs of conducting clinical trials [51].

Finally, some may object that providing additional benefits only to those who participate in clinical trials is unfair, and will reduce pressure to provide all individuals with access to healthcare services. To address this concern, it is important to ensure fair participant selection and not exclude potential participants because they are poor. In addition, those who participate in clinical trials represent only a tiny fraction of the total number of individuals who lack access to healthcare services. Hence, the present proposal offers a way to ensure fairness for participants today without disrupting the vital goal of ensuring healthcare access for all individuals.

Our proposal within the upcoming regulations in the European Union and the US

A new EU Regulation distinguishes trials that pose minimal additional risk (referred to as 'low-intervention clinical trials') from all other trials [52]. The former are typically phase 4 trials, where the investigational medicine is administered based on the summary of product characteristics approved by the regulatory agency, or is evidence-based and supported by published trials. The latter are typically phase 1, 2 or 3 trials of investigational medicines. We have argued that the reviewing research ethics committee should ensure that poor participants who lack access to health care should receive additional benefits to compensate for the risks and burdens posed by the trial, regardless of whether or not the trial is a 'low-intervention clinical trial'. For example, a low-intervention trial that involves many procedures (e.g. completing questionnaires) and visits to the research centre might pose significant burdens, even though it poses minimal additional risk. Similarly, since proposed amendments to the US Common Rule do not address the potential exploitation of poor participants who lack access to health care, the same approach could be used by institutional review boards in the US [53].

Conclusion

It is time to recognize and address the potential to exploit clinical trial participants living in North America and the

EU who are poor and lack access to healthcare services. However, providing these individuals with fair benefits is challenging precisely because they often lack access to healthcare services. We propose that regulators and interested stakeholders should revise current regulations and guidelines to recognize and address this concern. One possibility would be for sponsors to provide targeted additional benefits to these individuals, adopting a holistic approach to their disease or condition or non-medical needs. Regulators, sponsors, investigators, independent review committees and healthcare providers should act to ensure that all clinical trial participants are protected from exploitation no matter where they live.

Funding

The opinions expressed in this article are those of the authors and may not reflect the opinions of the organizations that they work for. Annette Rid received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007–2013) under REA grant agreement no. 301816. David Wendler is a NIH employee. The present work was funded in part by intramural research funds of the US NIH Clinical Center. However, the views expressed are the authors' own. They do not represent the position or policy of the NIH, the DHHS, or the US government.

Authors' contributions

R Dal-Ré conceived the idea and wrote the first draft of the manuscript. D Wendler and A Rid made substantial revisions; E Emanuel suggested further changes for important intellectual content. All authors approved the final version of the manuscript and are accountable for all aspects included in it.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no other relationships or activities that could appear to have influenced the submitted work, except for Prof. E Emanuel who declares being represented by the speaking group Leigh Bureau which frequently books him for paid speaking engagements across the healthcare spectrum.

Many thanks to Verina Wild, Institute of Biomedical Ethics, University of Zurich, Switzerland, for helpful comments on earlier versions of this paper.

References

1 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Fed Regist 1979; 44: 23192–7.

2 Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Biomedical Research Involving Human Subjects. International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS, 2002.

3 Lavery JM. The obligation to ensure access to beneficial treatments for research participants at the conclusion of clinical trials. In: The Oxford Textbook of Clinical Research Ethics, eds Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D. New York: Oxford University Press, 2008; 697–708.

4 Emanuel EJ. Benefits to host countries. In: The Oxford Textbook of Clinical Research Ethics, eds Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D. New York: Oxford University Press, 2008; 719–28.

5 Dal-Re R, Ndebele P, Higgs E, Sewankambo N, Wendler D. Protections for clinical trials in low and middle income countries need strengthening not weakening. BMJ 2014; 349: g4254.

6 Wertheimer A Exploitation in clinical research. In: The Oxford Textbook of Clinical Research Ethics, eds Emanuel EJ, Grady C, Crouch RA, Lie RK, Miller FG, Wendler D. New York: Oxford University Press, 2008; 201–10.

7 DeNavas-Walt C, Proctor BD, Smith JC. US Census Bureau, Current Population Reports, P60-245, Income, Poverty, and Health Insurance Coverage in the United States: 2012. Washington, DC: US Government Printing Office, 2013.

8 Sommers BD, Gunja MZ, Finegold K, Musco T. Changes in self-reported insurance coverage, access to care, and health under the Affordable Care Act. JAMA 2015; 314: 366–74.

9 Sommers BD. Health care reform's unfinished work — remaining barriers to coverage and access. N Engl J Med 2015; 373: 2395–7.

10 Piette JD, Rosland AM, Silveira MJ, Hayward R, McHorney CA. Medication cost problems among chronically ill adults in the US: did the financial crisis make a bad situation even worse? Patient Prefer Adherence 2011; 5: 187–94.

11 Daw JR, Morgan SG. Stitching the gaps in the Canadian public drug coverage patchwork? A review of provincial pharmacare policy changes from 2000 to 2010. Health Policy 2012; 104: 19–26.

12 Law MR, Cheng L, Dhalla IA, Heard D, Morgan SG. The effect of cost on adherence to prescription medications in Canada. CMAJ 2012; 184: 297–302.

13 Wellesley Institute. Who cares for the undocumented and uninsured? [online]. Available at http://www.wellesleyinstitute.com/health/who-cares-for-the-undocumented-and-uninsured/ (last accessed 19 August 2010).

14 Caulford P, D'Andrade J. Health care for Canada's medically uninsured immigrants and refugees: whose problem is it? Can Fam Physician 2012; 58: 725–7.

15 Karanikolos M, Mladovsky P, Cylus J, Thomson S, Basu S, Stuckler D, Mackenbach JP, McKee M. Financial crisis, austerity, and health in Europe. Lancet 2013; 381: 1323–31.

16 Kentikelenis A, Karanikolos M, Reeves A, McKee M, Stuckler D. Greece's health crisis: from austerity to denialism. Lancet 2014; 383: 748–53.

17 Rechel B, Mladovsky P, Ingleby D, Mackenbach JP, McKee M. Migration and health in an increasingly diverse Europe. Lancet 2013; 381: 1235–45.

18 Médecins du Monde. European Observatory on Access to Healthcare. Access to healthcare for undocumented migrants in 11 European countries. 2008 survey report. September 2009 [online]. Available at http://www.epim.info/wp-content/uploads/

2011/02/Access-to-healthcare-for-Undocumented-Migrants-in-11-EU-countries-2009.pdf (last accessed 8 February 2016).

19 Hall MA, Perrin J. Irregular migrants access to care: mapping public policy rationales. Public Health Ethics 2015; 8: 130–8.

20 Illingworth P, Parmet WE. The right to health: why it should apply to immigrants. Public Health Ethics 2015; 8: 148–61.

21 Médecins du Monde. Access to healthcare in Europe in times of crisis and rising xenophobia. An overview of the situation of people excluded from healthcare systems. April 2013 [online]. http://www.medecinsdumonde.org/Access-to-healthcare-in-Europe-in-times-of-crisis-and-rising-xenophobia (last accessed 8 February 2016).

22 Keith L, Van Ginneken E. Restricting access to the NHS for undocumented migrants is bad policy at high cost. BMJ 2015; 350: h3056.

23 McCarthy M Massachusetts may be nearing universal health coverage, preliminary data show. BMJ 2014; 348: g3938.

24 Rhodes KV, Kenney GM, Friedman AB, Saloner B, Lawson CC, Chearo D, Wissoker D, Polsky D. Primary care access for new patients on the eve of health care reform. JAMA Intern Med 2014; 174: 861–9.

25 Houston M Ireland considers compulsory health insurance for all and subsidised premiums for least well off. BMJ 2014; 348: g2718.

26 Morgan SG, Law M, Daw JR, Abraham L, Martin D. Estimated cost of universal public coverage of prescription drugs in Canada. CMAJ 2015; 187: 491–7.

27 Platform for International Cooperation on Undocumented Migrants (PICUM). Access to health care for undocumented migrants in Europe: the key role of local and regional authorities [online]. Available at http://picum.org/picum.org/uploads/publication/PolicyBrief_Local%20and%20Regional%20Authorities_AccessHealthCare_UndocumentedMigrants_Oct.2014.pdf (last accessed 8 February 2016).

28 Gray BH, Van Ginneken E. Health care for undocumented migrants: European approaches. Commonwealth Fund Pub 2012; 33: 1–12.

29 Hawkins JS, Emanuel EJ, eds. Exploitation and Developing Countries: The Ethics of Clinical Research. Princeton, NJ: Princeton University Press, 2008.

30 Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nat Biotechnol 2014; 32: 40–51.

31 Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries. Ethics: fair benefits for research in developing countries. Science 2002; 298: 2133–4.

32 Sofaer N, Strech D. Reasons why post-trial access to trial drugs should, or need not be ensured to research participants: a systematic review. Public Health Ethics 2011; 4: 160–84.

33 Shah S, Elmer S, Grady C. Planning for post-trial access to antiretroviral treatment for research participants in developing countries. Am J Public Health 2009; 99: 1556–62.

34 Haire B, Jordens C. Mind the gap: an empirical study of post-trial access in HIV biomedical prevention trials. Dev World Bioeth 2015; 15: 85–97.

35 Taylor HA, Merritt MW. Provision of community-wide benefits in public health intervention research: the experience of investigators conducting research in the community setting in South Asia. Dev World Bioeth 2012; 12: 157–63.

36 Molyneux S, Mulupi S, Mbaabu L, Marsh V. Benefits and payments for research participants: experiences and views from a research centre on the Kenyan coast. BMC Med Ethics 2012; 13: 13.

37 Ramjee G, Coumi N, Dladla-Qwabe N, Ganesh S, Gappoo S, Govinden R, Guddera V, Maharaj R, Moodley J, Morar N, Naidoo S, Palanee T. Experiences in conducting multiple community-based HIV prevention trials among women in KwaZulu-Natal, South Africa AIDS Res Ther 2010; 7: 10.

38 Pace C, Miller FG, Danis M. Enrolling the uninsured in clinical trials: an ethical perspective. Crit Care Med 2003; 31: S121–5.

39 Belsky L, Richardson HS. Medical researchers' ancillary clinical care responsibilities. BMJ 2004; 328: 1494–6.

40 Fisher JA, Kalbaugh CA. United States private-sector physicians and pharmaceutical contract research: a qualitative study. PLoS Med 2012; 9: e1001271.

41 European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on compassionate use of medicinal products, pursuant to article 83 of regulation (EC) No 726, 2004. Doc Ref. EMEA/27170/2006 [online]. Available at http://www.ema.EUropa.EU/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf (last accessed 19 July 2007).

42 US Food and Drug Administration. Final Rule. 21 CFR parts 312. Expanded access to investigational drugs for treatment use. Fed Regist 2009; 74: 40900–45 [online]. Available at http://www.gpo.gov/fdsys/pkg/FR-2009-08-13/pdf/E9-19005.pdf (last accessed 8 February 2016). Expanded access (compassionate use) [online]. Available at http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionatEUse/default.htm (last accessed 8 February 2016).

43 Health Canada. Special Access Programme [online]. Available at http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php (last accessed 8 February 2016).

44 Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005–2012. JAMA 2014; 311: 368–77.

45 Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HM, Ross JS. Regulatory review of novel therapeutics – comparison of three regulatory agencies. N Engl J Med 2012; 366: 2284–93.

46 Whitfield K, Huemer KH, Winter D, Thirstrup S, Libersa C, Barraud B, Kubiak C, Stankovski L, Grählert X, Dreier G, Geismann S, Kuchinke W, Strenge-Hesse A, Temesvari Z, Blasko G, Kardos G, O'Brien T, Cooney M, Gaynor S, Schieppati A, Serrano M, de Andres F, Sanz N, Hernández R, Kreis G, Asker-Hagelberg C, Johansson H, Asghar A, Husson JM, Demotes J, Gluud C Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries. Trials 2010; 11: 104.

47 National Health Service Health Research Authority. Care after research: a framework for NHS RECs [online]. Available at http://www.hra.nhs.uk/resources/during-and-after-your-study/care-after-research/ (last accessed 8 February 2016).

48 Casarett D, Karlawish J, Sankar P, Hirschman KB, Asch DA. Open label extension studies and the ethical design of clinical trials. Hastings Center Report 2001; 23: 1–5.

49 Emanuel EJ, Currie XE, Herman A, Project Phidisa. Undue inducement in clinical research in developing countries: is it a worry? Lancet 2005; 366: 336–40.

50 Largent E, Grady C, Miller FG, Wertheimer A. Misconceptions about coercion and undue influence: reflections on the views of IRB members. Bioethics 2013; 27: 500–7.

51 Adams CP, Brantner VV. Spending on new drug development. Health Econ 2010; 19: 130–41.

52 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union L 158/1-77, 17 June 2014. [online] Available at http://ec.Europa.EU/health/files/Eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf (last accessed 8 February 2016).

53 Federal Policy for the Protection of Human Subjects. Notice of Proposed Rulemaking. Fed Regist 2015; 80: 53931–4061. [online] Available at https://www.gpo.gov/fdsys/pkg/FR-2015-09-08/pdf/2015-21756.pdf (last accessed 8 February 2016).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.12879/suppinfo.