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Standards, Harmonization and Cultural Differences: Examining the Implementation of a European Stem Cell Clinical Trial

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Abstract

A complex set of European regulations aims to facilitate regenerative medicine, harmonizing good clinical and manufacturing standards and streamlining ethical approval procedures. The sociology of standardization has elaborated some of the effects of regulation but little is known about how such implementation works in practice across institutions and countries in regenerative medicine. The effects of transnational harmonization of clinical trial conduct are complex. A long-term ethnographic study alongside a multinational clinical trial finds a range of obstacles. Harmonization standardizes at one level, but implementing the standards brings to the fore new layers of difference between countries. Europe-wide harmonization of regulations currently sdisadvantages low-cost clinician-lead research in comparison to industry-sponsored clinical trials. Moreover, harmonized standards must be aligned with the cultural variations in everyday practice across European countries. Each clinical team must find its own way of bridging harmonized compulsory practice with how things are done where they are, respecting expectations from both patients and the local hospital ethics committee. Established ways of working must further be adapted to a range of institutional and cultural conventions that affect the clinical trial such as insurance practices and understandings of patient autonomy. An additional finding is that the specific practical roles of team members in the trial affect their evaluation of the importance of these challenges. Our findings lead to conclusions of wider significance for the sociology of standards concerning how regulation works and for medical sociology about how trial funding and research directions in stem cell medicine intersect.

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'Standardization is an active, time- and resource-intensive process. Depending on the standard, building standard-based societies may require integration of many different levels: from national cultures with their moral orders to institutions with their conventions of work practices, organizations, and multiple layers of technologies. … Very few standards work as intended by the designers of standards because they are tinkered with, whether slightly or fundamentally. It would be wrong to consider these standards as failures because a standard's flexibility is often key to its success.'

(Timmermans and Epstein, 2010, p. 81)

1. Introduction

There is much public debate and professional concern about the costs and amount of time it takes for new therapeutics to come into the clinic. European regulations aim to address this problem by harmonizing the standards for clinical trials that provide evidence for the effectiveness of new treatments across all EU countries. Standardization aims to simplify and speed up innovation and approval processes in order to facilitate the rollout of new therapeutics across the EU.

Randomized control trials (RCTs) are widely used as a gold standard in medical research, although the limits of methodology have been criticized over the past decades (Cartwright, 2007; Will, 2007), and other protocols to test new therapies have been developed, such as hospital exemptions in the case of rare diseases (Salter et al., 2014). But the RCT is still the dominant method of scientific validation in the clinic. To test a new drug or treatment on thousands of patients, inclusion-criteria for a trial are defined, according to which the patients must be similar in relevant characteristics. In relation to these internal validity criteria, the proportional success of the new treatment can be measured. The trial protocol narrowly defines the group of trial patients approached, how the tested medical innovation is administered and how its clinical efficacy is monitored. Half of the patients receive the new treatment, the other half are treated according to the best current standard care. All patients are followed up according to the agreed protocol.

An inevitable tension exists between keeping the patient group as narrowly defined as possible (internal validity) and showing the efficacy of the new treatment across different communities (external validity). The internal validity criterion has been prioritized in regulations and standards to harmonize multinational trials in the EU. Striking the balance between keeping a trial feasible and specific for scientific validity and producing

generalizable results is tricky and open to critique. Patient groups and treatment protocols must be sufficiently standardized to measure the clinical efficacy of the new treatment, i.e. the trial outcome, whilst including a varied patient population, ideally from diverse socio-economic groups and different cultures. This article highlights how different cultural conventions and practices intersect and affect the pragmatic running of a trial, not least in terms of time and cost.

The trial reported on will be referred to as BAMI.[1] BAMI is an ongoing phase-III clinical trial conducted across ten EU countries. Our sociological research segment, entitled 'Toward Harmonized Ethical Standards', work package 7 in BAMI, concerns the effects of unified protocols on trial conduct across the participating clinics, especially the hurdles the teams have had to overcome in order to gain trial approval and start recruiting patients to the trial. The focus on the implementation of the trial and the empirical findings emphasizes that recruiting the required patients for such a trial may itself be a matter of the success of professional clinical practice on top of the clinical efficacy of the trialled treatment, the success of which cannot be assessed at the time of writing.

This article addresses the following questions:

- How do common trial protocols and approval processes affect work locally?
- What were the national-level implications of aligning every team's actions to follow a set of shared international rules?
- What cultural differences have affected BAMI?

Our findings illustrate that multinational trials are very difficult to conduct in practice, even if a shared regulatory framework is in place. European countries differ vastly in health care provision and insurance systems, but also in routine patient-doctor interactions, language, aspects of lifestyle and the role of the family in medical decisions. However, they share the same routine treatment for acute myocardial infarction (AMI) and how it is administered.[2] Concerning clinical practice, a trial such as BAMI should thus be easy to implement – given

[1] An abbreviation for: 'The effect of intracoronary reinfusion of bone marrow-derived mononuclear cells (BM-MNC) on all-cause mortality in acute myocardial infarction'. BAMI is a Phase III clinical trial led by clinician scientists and funded by the European Commission's FP 7 Health programme.

[2] Largely due to standardization by medical organizations, treatment of AMI follows best practice guidelines set out by the European Society of Cardiology.

that EU regulation streamlines the process. Yet the influence of cultural differences has become an important problem in running the trial.

The new EU regulations on the implementation of clinical trials bring to the fore a novel array of problems regarding cultural differences between trial locations. Multinational trials have to align each participating team to the same set of rules of conduct. This means that customs of place or institutional arrangement have to be either altered locally or passed on to every other participating country.

Our conclusion points out two aspects of wider significance for the sociology of standards and regulation. The first concerns the particular difficulties facing staff managing highly regulated multinational academic trials; the second, the intersection of trial funding and research directions in stem cell medicine.

The effects of the new harmonized regulations are poorly understood and the lack of uptake of the Voluntary Harmonisation Procedure (VHP) by industry trial sponsors troubles EU policy makers. Following standardization, cultural differences previously negligible to multinational clinical trial practice can delay or disrupt trials. This challenges the general endorsement of regulatory harmonization as a method of achieving faster clinical translation of the science. It also brings to light a theoretical question concerning the power of select standardization as a technique to reshape particular practices woven into the complex web of multiple differences in and between nations and communities.

Below we shall provide some background to the debate on harmonized regulation and standards in biomedical innovation and introduce our methodology, before we present findings on cultural differences – especially problems arising from varied practices of insuring patients and the ways of managing language and communication with patients.

2. Analytical perspectives

Standardization has been a key instrument for shaping Europe as a unified economic area across which innovations can be rolled out. The benefits of standards for European industries are extensive and include helping manufacturers reduce costs, anticipate technical requirements, increase production capacity and markets, and speed up processes of innovation. The European Commission endorses these positive effects of standards in areas

such as trade, the creation of a single market for products and services, and innovation (European Commission, 2016).[3]

Social science and, more recently, Science and Technology Studies in particular, have taken to examining standards and regulation. Susan Leigh Star's studies from the 1990s (Star 1991, 1995; Bowker and Star 1999; Lampland and Star, 2009) laid the foundation for a critical sociology of standardization explored further by many scholars, including Stefan Timmermans and Marc Berg, on whose findings we draw. Timmermans and Steven Epstein published a review of the topics covered in the sociology of standards and standardization (2010), distinguishing between design standards and standardization of processes and the specific challenges encountered in standardizing clinical practices of diagnosis and treatment. They highlight problems concerning the implementation of procedural standards, the unpredictability of outcomes and side effects, and the role of experts and professional interests in standard setting. 'To coordinate diverse interests and activities, standards necessarily delegate some residual work that requires active participation and submission of people to the standard's directives. Tinkering, repairing, subverting or circumventing prescriptions of the standards are necessary to make standards work.' (p. 81)

Adding to this discussion of standardization, which is often quite abstract, our case study examines how standardization of cell therapy research in Europe affects clinical trial implementation and how local practices are adapted in order to comply to these standards, making them work. The overlapping sets of existing standards encountered in this multinational trial involve not only differences in health care system organization across Europe and other related institutions, but also the great differences in cultural and national attitudes towards stem cell research, which in turn have received a lot of attention in literature (see for example Jasanoff, 2005; Bender et al., 2005; Salter, 2007; Beltrame, 2014). Following wide-ranging harmonization of these regulations of research, however, new layers of difference between institutional practices from both within and outside the clinic and the laboratory have been found to affect stem cell clinical trial conduct and it is these cultural differences and how they affect practice at the stage of implementation that we focus on.

[3] The benefits of standardization according to the European Commission webpages, available at: http://ec.europa.eu/growth/single-market/european-standards/policy/benefits/index_en.htm (Accessed 30 May 2016).

Biomedical innovation is, in some aspects, a special area of standardization because its objective is to improve human medical care and thus it is charged with expectations beyond mere economic benefit. The research field is often seen as critical for individual wellbeing and future material and social wellbeing in advanced economies. Common standards have accompanied the development of biomedicine and have been increasingly formalized from professional standards to mandatory official regulations (Cambrosio et al., 2009). A European platform for RCTs in cell therapy and regenerative medicine has been developed. Decisions regarding RCTs are shaped by both risk awareness and risk avoidance. These include technological and economic risks as well as risks regarding the efficacy of therapies (Faulkner et al., 2008).

Annually, between 4000 and 6000 applications for randomized clinical trials are submitted to ethics committees across Europe (European Commission, 2009). The variation in assessment of these applications has led to concerns about the future of clinical trials (Cressy, 2010; Hartmann and Hartmann-Vareilles, 2006; Hunter, 2011). Member states set up competent authorities to approve clinical trials with their own regulations for monitoring Good Clinical Practice (GCP), reporting serious adverse events, and insuring trials (Hartmann, 2012). Thus, the ethical approval procedures for the same scientific clinical trial protocol often require country-specific alterations to that protocol.

In order to overcome this diversity, the EU Clinical Trials Directive (European Commission, 2001) streamlined rules of assessing clinical trial applications across member states. The aim was to foster equality in patient care and treatment standards, and the timely implementation of future therapies (European Commission, 2007; Garattini, 2009).

The BAMI trial has to follow these procedures and regulations. In addition, using stem cells, BAMI also has to comply with the regulations of the European Tissue and Cells Directive (European Commission, 2004). New regulation is often ambiguous when first implemented. Stephens and colleagues have introduced a notion of "never-ending regress whereby scientists have to provide increasingly more guarantees that protocols have been followed, standards reached and maintained, and rules adhered to" (Stephens et al., 2013, p. 346). That was the case also with the EUTCD, which was complemented with two technical directives in 2006 that refined which practices are in line with it the EUTCD and its Good Manufacturing Practice and Advanced Therapy Medicinal Product standard.

Empirical studies have shown that the directive had in practice been implemented differently

in different European countries (Veerus et al., 2014; Weber et al., 2010), which affected clinical trials similar to BAMI (Wilson-Kovacs et al., 2010). Wilson-Kovacs and colleagues have shown that managing ambiguous new regulations and sorting out their application is a practical accomplishment. They compared UK and German implementation rules of the EUTCD and found that the implementation practice in the UK enabled and required UK-based stem cell researchers to negotiate with the regulator the status of a specific use of cells. In Germany, the implementation rules were applied more uniformly and strictly, requiring high laboratory processing standards, which led to the widespread upgrading of laboratories years before the unified implementation rules the EUTCD put in force in 2010 forced all laboratories in Europe working with human tissues and cells to upgrade and comply with new higher standards as well.

The harmonized implementation rules for the EUTCD can be seen as preventing further such negotiations and ending the regulatory regress. Since that step, all trials using stem cells in innovative ways and in non-homologous tissues have to apply Advanced Therapy Investigative Medicinal Products (ATIMP) standards of GMP.

For a multinational trial this means detailed monitoring practices have to be in place to make sure that all research partners are fully compliant with the trial protocol. The BAMI trial protocol had to be approved by the UK Medical Health Research Agency, acting for the European Medicines Agency, which oversees the implementation of the Directive.

ATIMP compliance had severe consequences for BAMI, affecting its logistics and financial position, and undermining the commitment of some partners to remain active in the trial. Several partners (and thus countries) dropped out for different reasons, believing that the trial was unattractive or unfeasible under these conditions. The positive goals of these regulations and the problems they bring can be described through three different dimensions: a) increasing scientific efficacy, b) timely patient recruitment, and c) problems involved in getting various everyday practices to align the best clinical practice with local cultural expectations (what we call ‘cultural issues’). These three aspects are intertwined, as will be explained below before we concentrate on the presentation of our findings regarding dimension c). For this analysis, we draw on the theoretical concepts developed in the sociology of regulation and the existing discussion of clinical trials in regenerative medicine in medical sociology.

a) Scientific efficacy in clinical trials

Why, one might ask, would anyone opt to conduct something as tightly controlled as a clinical trial across several countries? Problems due to different traditions, health care systems, and so on, will almost inevitably arise – which could be reduced, if not avoided, by choosing a location as homogenous as possible. However, the fact that a new drug or treatment works in one local social context does not show its general clinical efficacy. The generalization from a trial neglects local factors influencing treatment outcome – clinical trial results do not readily apply to all humans (Rothwell, 2005; Petryna, 2009; Will and Moreira, 2010).

Many aspects of standard patient care vary vastly between rich and poor countries, and between cities and rural areas. Similarly, nutritional factors, life-style habits, general socio-economic conditions, the involvement of non-professional family carers, and so on, can influence patient recovery. Such cultural factors cannot be standardized or measured in a trial protocol, and consequently, findings from only one specific health care environment and cultural context are not readily generalizable. Clinical trial findings need to be validated trans-culturally. The distinction between internal and external validity (Campbell and Stanley, 1963) addresses this epistemological issue. The utility and validity of RCTs has further been challenged because pharmaceutical companies focus on first-world health care issues (Nwobike, 2006), and stem cell therapies mostly target life-style-related diseases of the wealthy (Anele, 2008).

Globalization has highlighted the problems with external validity. For reasons of fairness, new therapies should be developed and made available to people regardless of where they live. This ethical and epistemological problem has an economic side, too. If the validity of a trial is limited, so is the health utility of the drug or intervention and the potential gain for pharmaceutical businesses and the wider economy (Sunder Rajan, 2010). It matters for all stakeholders that the tested stem cell treatment is effective despite the vast differences in disease appearance, in economic conditions, and in the cultural practices that constitute and intersect with health care provision.

b) Patient recruitment and disease specificities

A second parallel development shaping the need for regulatory standardization is the increasing need for very large populations to recruit participants for clinical trials (Anderson, 2003; Epstein, 2007). Current STS scholarship discusses this issue in relation to rare or orphan diseases (Hollak et al., 2016), yet, even for very common conditions such as AMI,

recruitment for a large trial can be an issue. The biomedical sciences have increasingly perceived differences within what previously seemed to be just one disease.

Treatments for common diseases in the West have improved greatly over the past decades and current science targets more and more narrowly defined subtypes of health conditions. If a treatment is tested not on all patients with breast cancer or AMI but only on those with a rather specific form of the condition, it becomes harder to find the thousands of patients needed for a phase III clinical trial in a patient population. This numerical issue is heightened in RCTs where half of the patients receive standard treatment.

Moreover, RCTs must proceed quickly. They cannot go on for a decade or more, as any improvement to the standard of care in the meantime would change how patients ought to be cared for and thus undermine either the clinical or epistemological validity of the trial. Although a major cause of death in Europe, finding many AMI patients with severely restricted heart function after primary coronary angioplasty in eleven European countries over three years, even if through a large network of clinics, seemed a challenging undertaking before BAMI even started. None of the clinicians in the trial deemed it feasible to recruit the patient number needed in clinics in the UK, Spain, Italy or Germany alone.

c) The relevance of cultural differences within and beyond the clinical institutions

Present concepts and theoretical literature often regard harmonized regulation as the pathway to more shared practice. However, in that very process of standardization, previously unproblematic cultural differences between countries become problematic. Over the past decade, an expansive body of literature in STS has illustrated the importance of regulation in biomedicine (Timmermans and Epstein, 2010; Cambrosio et al., 2006). Cambrosio and colleagues dedicated a special issue of *Social Studies of Science* to their concept of regulatory objectivity and biomedical conventions (Cambrosio et al., 2009). Helpful analysis on the difficulties of agreeing and implementing standards that can be implemented with the desired effects are provided by Patrick Castel in oncology research in France (2009), and by Linda Hogle's reflections on pragmatic objectivity in the standardization of engineered tissues in the US (2009). Other detailed studies focussed on European regulatory policies regarding stem cell research and medicine (Salter, 2007; Salter and Salter, 2013), and the spread of ethical governance via regulation in non-Western countries (e.g. Rosemann and Sleeboom-Faulkner, 2016; Waldby and Salter, 2008).

Timmermans and Epstein argue that the sociology of standards has shown that 'Standardization is an active process that aspires to stability and order. Any order is a hard-won achievement that requires the submission of diverse actors. Standardization consists of building a society around a standard with an implied script that brings people and things together in a world already full of competing conventions and standards' (2010, p. 84). The recent systematic approach to streamlining regulations for clinical trials (described above), the use of cells and tissues in science and medicine, as well as the requirement for national competent authority approval, all aim at comprehensive regulation of the biomedical sector in Europe – which is already shaped by national regulations and local practices of compliance, but also diverse health care environments, ethics and attitudes to what is good medical care. Thus, in everyday clinical practice these European regulations intersect with a range of standards and cultural conventions in diverse areas of social organization. The standard neither encounters nor produces a standardized world.

In order to fit diverse practice into this levelled regulatory plane, the actors need to develop creative solutions in order to achieve compliance with the European regulations and national and local expectations and practices. These local solutions vary according to the differently organized institutions, expectations and practices in the participating national cultures. Harmonization achieves shared practice of all trial practitioners in all the details standardized, yet via different adaptations of routine and locally compliant practice. This tinkering and active problem-solving is essential for running methodologically credible trials across cultures and nations with different institutional settings.

Some major problems BAMI encountered arose directly from regulation (Hauskeller and Baur, 2017), yet other problems did not arise from regulation *per se*, but from its implementation across diverse interrelated conventions and practices at national and regional levels. Below we report on how standardization emphasizes the impact of cultural differences not directly related to the clinical protocol on trial conduct. We discuss what, from the clinical perspective, appear to be largely 'external' factors. They are, however, so closely entangled with clinical practice that they can uphold or disrupt the timely implementation and daily running of a clinical trial. Yet they are outside the scope of regulations for the clinical environment and are unlikely to become subject to standardization any time soon. External factors include insurance practices, and attitudes to patient consent and to expert-client communication and responsibilities.

BAMI had to comply with formal regulations such as ATIMP but it also was the first large trial to use the new Voluntary Harmonisation Procedure (VHP). This procedure promises to reduce regulatory hurdles before patient recruitment can begin (Baeyens, 2004; Lemair and Baeyens, 2002). Observation of the process of VHP approval in BAMI found the procedure falling short in the key aspect it promised to address, namely speedy approval across the participating countries. The VHP, too, was subject to regulatory regress and transformation, whilst BAMI has been undergoing repeated re-approvals within its framework. This aspect cannot be detailed in this article but it added to the overall complications faced in the implementation of BAMI.

3. Methodology

We have been recording and analysing the effects of European harmonization policies on the BAMI adult stem cell clinical trial. Being a Principle Investigator (PI) on the BAMI grant and project, Hauskeller has been observing BAMI from the funding application to trial completion – now expected for 2019, two years after the last patients will be recruited. Using interviews and mini-surveys with team members, we collected a wide range of experiences and perspectives from inside the large team. This article reports on the obstacles for trial implementation and day-to-day business that emerged after initial VHP approval for the trial was gained in 2013.

Data collection began with a mini-survey to establish the attendees' initial views on the BAMI trial process at the BAMI 'Kick-off Meeting' in London, where the sociology work package was introduced to the teams (primarily the BAMI Consortium partners). A brief questionnaire was handed out to be filled in then and there. The attendees were asked to reflect and list issues with ethics approval encountered in previous trials, and to state whether they expected any problems with approval for BAMI. 14 partners from 8 countries – Denmark, Spain, UK, Germany, Italy, Norway, Belgium and the Czech Republic – were present. No respondent in this survey expected any problems with BAMI. Potential approval issues from other trials had been met and solved locally. These local solutions were then discussed around the table, because they would all have to be taken into consideration in the preparation of the unified VHP approval for BAMI to ensure ready acceptance of the protocol by the national competent authorities.

In 2014/15, we conducted 28 interviews, 25 with clinical staff (e.g. PIs, NCCs, cardiologists, study nurses), and 3 with project managers responsible for trial-wide infrastructure

(insurance, centralised echo-cardiography, patient randomisation). Interviews lasted for 30 to 60 minutes, following a pre-defined topic guide. The interviews were recorded on tape and transcribed. At this stage of BAMI the teams could report on their experiences with local implementation. Interviews were conducted face-to-face, via Skype or telephone.

As the BAMI partners were spread across Europe, interviewing via telephone or Skype allowed for the collection of data when face-to-face interviewing was not possible. It limited excessive travelling, with the consequent high cost in researcher time and negative environmental effect (Hanna, 2012). The little discussion on the use of Skype over telephone interviews presents arguments in favour and against, referring to similar discussions contrasting telephone and face-to-face interviews (Irvine et al., 2013; Oates, 2015).

An advantage of face-to-face interviews is that they offer superior rapport with the interviewee (Stephens, 2007; Holt, 2010) and thus possibly increased quality of the collected data. Oates, however, found qualitative comparability and relevance to the research questions between face-to-face and over-the-telephone data collection (2015). Carr and Worth (2001) point out that telephone interviews have fewer pronounced face-to-face interviewer effects – when the personality and behaviour of the interviewer influence the behaviour and responses of the interviewee. In contrast, Oates (2015) points out that telephone interviews tend to be shorter with more requests for clarification from the researcher and more checks from interviewees for adequacy in their responses. Consequently, as researchers we expressed a preference for face-to-face interviews when feasible, but left the choice between telephone or webcam enabled Skype to the interviewees, when face-to-face interviews were not feasible.

The interview questions were based on findings from the participant observation of regulatory approval processes and pilot interviews. Data collection and analysis proceeded in parallel. Some initial findings required further data collection and the return to early interviewees. Interview materials were transcribed and the data analysed using conventional methods supported by NVivo (Version 10). Keyword searches helped to identify themes and categories. Entirely electronic-based analysis seemed unsuitable, not least because most interviewees were not native speakers of English and might have used language in non-standard ways. Also, some interviews had been conducted in other languages (viz. German and Spanish) and we translated interview passages that we used in publications.

Following analysis of the interview data, we used a ‘finding check’ mini-survey at a partner meeting on 12 February 2015 and forwarded it to BAMI team members unable to attend,

including study nurses. The aim was to collect responses to, and validate our interpretation of, the findings hitherto. 22 respondents from 9 countries commented in this format on how they judged the relevance of our findings. The feedback confirmed we had identified all the problems of which respondents were aware, and at the same time it showed an unexpected discrepancy in the assessment of the seriousness of the different problems. The dramatic effects of the changes in the implementation of the EU Directive on BAMI were agreed upon by all respondents.

With regard to the importance of the findings we describe in this article, we note that respondents disagreed markedly on local cultural issues. Some of the senior clinicians were not aware of them, others did not regard them as relevant obstacles. Yet many clinical staff at NCCs had highlighted these issues as major hurdles with which they had struggled in the day-to-day running of the trial. The study nurses in particular stressed how much time and money went into addressing cultural expectations in relation to trial insurance, language and communication. This discrepancy in how PIs and NCC members rated the influence of cultural issues will be considered after the relevant findings.

4. Cultural Issues

In this section we present our findings on the external factors or cultural differences that cause problems and that have to be aligned with the overall regulatory framework in which BAMI must operate. These cultural issues are obstacles that affect individual sites or countries and arise from their particular situations, conventions or local regulations. They are not regulated in the EMA and VHP approval procedures.

Situated outside direct EU clinical trial governance regimes, cultural differences become more obvious and cause problems during the trial implementation phase and in day-to-day conduct. They are confronted and solved by the staff running the trial in the clinic, i.e. primarily study nurses. Below we present examples of what we call cultural issues caused by local differences in practices between European partner countries.

The 'Good Clinical Practice' (GCP) certificate

According to the EU-Directive 2001/20/EC, which is legally binding, anyone working on a clinical trial needs to have the GCP certificate confirming they have passed a particular training module on the subject. The sponsor of BAMI is in the UK, where it has become best clinical practice to expect that the GCP module needs to be passed and the certificate re-

issued every other year for everyone conducting clinical trials. Whilst the certificate as such is now compulsory across Europe, its biannual refresher is not. Yet, because BAMI followed the ethical practices put forth by the UK sponsor, all partners were formally compelled to comply with the UK practice of implementing the EU GCP certification.

Every clinical team member in BAMI had to present a GCP certificate dating from within the past two years. This raised issues in three cases: two senior physicians with many years of clinical and trial practice were requested to attend a training module before their team was allowed to start in BAMI. The physicians resisted for a while, arguing they were obviously GCP qualified – given their experience – and thus did not need to do this: they eventually took the module and obtained the certificate. In a third country, the PI was in possession of a GCP certificate, dating from more than a decade ago and was reluctant to comply with what seemed a mere formality. The resistance resulted in a delay in some site initiations and was experienced as distressing by the study nurses who had to convince the respective physicians to acquire the certificate by completing the online module provided by the sponsor. As sociologists we saw power issues at play here, both among and within the clinical teams, and our interview data support this interpretation – but as such this is not an original finding.

Insurance of the patients in the trial

When the PIs applied for ethics application through VHP, the worldwide insurance policy with standard annual policy renewal was put in place at the sponsoring lead institution, Queen Mary University of London. The trial was covered for what is standard UK practice to run such a clinical trial in Europe and worldwide. However, in the process of obtaining competent authority approval in the partner countries, it became evident that different countries within Europe require additional local insurance because they have different laws and traditions regarding insurance policies that affect clinical trial insurance.

In the UK it is common for many insurance companies in the private and institutional sector to issue one-year insurance contracts, renewable annually. In other partner countries, different attitudes to how insurance ought to operate make good sense within their established framework. In Italy, for example, university research hospitals fall into a special insurance category, whereas non-university hospitals and their risks are classified separately:

> “In Italy we also had to sign extra insurance for the patients enrolled in the BAMI. And actually, this is another issue that will come up shortly because in the insurance

> we have covered the total number of patients that we enrol, that is 125, but what we paid actually covers just one centre or university hospital, so we are now negotiating the insurance because if we open satellite hospitals in the next months, although the number of patients that we cover will be the same, it's most likely that there will be an increase in costs for us. The insurance will ask us to pay more, simply because they are not qualified hospitals, I mean, like our hospital. So, there are some issues that we are negotiating now." (NCC, Italy)

In Germany, the ethics committees argued that every patient needs to be insured for as long as she or he is in the trial. Not least because, in case harm is experienced by a patient, it might be extremely difficult to get the trial insurance renewed. The insurance provided for each patient has to cover the whole period during which the patient is in the study. As this service was not provided by the BAMI sponsor, the German team had to arrange its own insurance at a cost of an additional €15000 plus VAT for the first 300 patients recruited. Because of this high and unexpected cost, the German NCC has so far only insured a smaller number of patients than they expect to recruit and will have to add to the insurance in accordance with recruitment numbers.

> "The English patient insurance is totally insufficient in Germany. The ethics committee stated they cannot accept it, because in England insurance can be cancelled after one year. The problem the German ethics committee has with this is that if an insurance case were to happen, and subsequently no insurance company wanted to continue insuring the trial, then the patients in BAMI would no longer be insured. … I then agreed an additional insurance via the sponsor and the sponsor signed it." (PI, NCC, Germany; translation CH)

Apart from the financial burden, it seems that other connected issues would have resulted in problems with insurance anyway, issues that can now be addressed in the separate additional insurances set up. The reason is that there are other country-specific ethical requirements of insurance not covered by the BAMI general insurance. Our interview analysis and a comparison of Patient Information Sheets showed that for example in Spain, Italy, and Germany, patients have to be able to contact the insurance provider directly.

In the UK patients can contact the hospital trust where they were treated, which would then contact the sponsor, and the sponsor would contact the insurer. In Germany, Italy and Spain, good ethical practice requires that a local office and phone number for the insurance covering

the trial is on the Patient Information Sheet so that patients can contact the company directly. Again, there are differences in the details provided to trial participants. In Germany the full postal address including telephone number and an email address have to be available to patients. The Spanish authorities, in contrast, provide the number of the insurance policy and the name of the insurance company, but no contact details. Instead, they encourage patients to get in touch with the doctor in the first instance. Documents originating in the United Kingdom follow the standard National Health Service (NHS) complaints procedure, directing patients to the Patient Advisory Liaison Service, for which there is no direct equivalent in many other partner countries.

Increasing risk-awareness also meant that many NCCs required the BAMI insurance policy to be translated into their own language to be checked by ethics authorities, something that comes at a cost. BAMI coordinating staff at Queen Mary University of London support NCCs in their efforts to comply with their particular insurance requirements. But they reported that it is often hard for them to gauge what exactly needs to be done and to whom they need speak. Conversely, NCC staff and PIs in the hospitals expect the team at the sponsoring institution to know about these issues because they are not experts in details of insurance either.

What needs to be insured and how patients are informed differs across the BAMI partner countries according to local cultural conventions and ethical perceptions. Knowledge about these differences is not readily available within the clinical research environment. Insurance issues and the other cultural issues would not be confronted if the teams participated in a commercially sponsored and funded trial. An industry sponsor would take on the task of figuring out solutions to insurance and other problems the clinical teams have had to solve in BAMI, managing problems centrally with hired experts. Conducted by hospital physicians without such a sponsor, the BAMI trial did not have a comparable infrastructure of experts to fall back on. The unexpected problems arising from these local differences have been described as disheartening at times by some members in the clinical team.

Problems with Language Diversity

Several clinical trial nurses nominated language barriers as a big problem, particularly in hospitals in international cities such as Frankfurt, London, Rome, and Madrid, where many inhabitants and visitors do not speak the local language sufficiently well to communicate clearly in the acute clinical situation of an AMI. Language issues are relevant in two contexts

– informed consent procedures, and day-to-day communication – and as such have been not a central but certainly a persistent topic in relation to clinical best practice (Betancourt and Jacobs, 1972; Schenker et al., 2008).

Certainty about clear communication is required when establishing whether a patient fully comprehends the trial and what they agree to participate in. In order to ensure ethical conduct and informed consent, the clinical team must judge the patient's ability to consent. To give valid consent to participate, patients must not only possess the mental capacity to consent, but they must also be sufficiently informed about the trial and what it entails. They must be assured that participation is voluntary and that declining does not affect their treatment negatively. Studies have shown that in stressful situations such as that following a severe heart attack, patients' cognitive function can be impaired to the extent that they are unable to fully comprehend the details of a trial in which they are asked to take part (Gammelgaard et al., 2004a; Gammelgaard et al., 2004b). This situation can be aggravated through language barriers (Howard and de Mets, 1981; Kucia and Horowitz, 2000).

For a multinational trial, a certain level of variety in patient languages should be easily managed because Patient Information Sheets have been prepared in all the primary languages of the countries participating. However, the English language sheet cannot simply be used in Madrid, Rome or Frankfurt because the content that needs to be covered differs in response to local ethical expectations, such as the insurance issue above. The Patient Information Sheet of each country needs to be translated anew, at least in the diverging sections. These translations must be carried out by a certified medical translator, and in some countries the resulting document needs to be approved by the relevant ethics committee. Therefore, recruiting patients who are not confident speakers of the local language costs time and money. Nevertheless, a study nurse we spoke to confirmed that every effort is made to include all eligible patients in the trial.

> "The only problem is the language barrier. It's always difficult, if we don't understand the patients – we have to translate them, but of course, the patients are included in the study. … We have a list (of interpreters), but actually, you ought to get consent in their mother tongue. And you always have to ensure that the interpreter is neutral and translates exactly what you are saying – you never know what they tell you and whether they translate verbatim. I'd find it helpful to have patient information sheets in English." (Study Nurse, Germany; translation NB)

The second aspect concerns day-to-day communication with the patients during the trial. Although the hospitals in the study have access to interpreters, it has happened that patients cannot be included because they speak a language for which no interpreter is available at short notice – and recruitment has to happen within a day after standard AMI treatment.

> "If they do not speak the language, you cannot assess them properly and then also you have to make sure that a family member is there with them to do the translation and tell you how they feel. So, that's why we found it very difficult to recruit them …" (Study Nurse, UK)

Interpreters also have to be in attendance at every check-up, which is usually done over the phone. The logistical and financial effort involved because of ethical and language requirements limits the recruitment of patients insufficiently versed in the local language.

The regulatory and ethical-approval related problems in the everyday running of a trial such as BAMI are manifold and vary between countries and even between hospitals in a country. Yet the perception of these challenges, too, varied amongst BAMI team members, markedly between senior cardiologist PIs on the one hand and study nurses and country coordinating teams on the other, as we found in our mini-survey where findings were checked by participants.

Shared practice across a trial is required scientifically and harmonized regulation across Europe aims to improve the conditions for rapid and reliable clinical translation of stem cell science. Yet, alongside the equal position in which all project partners have to work, cultural differences make themselves felt and appear as local challenges to achieving this equal position whilst conforming to local expectations. Diverse effects of cultural differences in terms of ethical or institutional practices appear when actions previously not formally standardized become regulated in clinical trials. Different societal institutions such as insurance practices and cultural conventions affect the smooth running of the trial, given that the trial needs to balance two different sets of expectations: harmonized European standards and local necessities of doing things in a certain way.

The most obvious problem for BAMI was the reclassification of its particular stem cell application under the rules for ATIMP. This required access to laboratories licensed to produce Investigative Medicinal Products to GMP ('Good Manufacturing Practice') standards, which in 2011 was a relatively new and not widely available accredited process.

Problems with access to such laboratories locally meant that BAMI had to cover the huge costs for transporting cells around Europe, again in a manner conforming to ATIMP requirements. Less obvious problems arose following the BAMI team's compliance with the EU's VHP protocol.

Drawing on empirical data and the sociological literature on regulation, we have illustrated what standardization in a non-standard world may mean, in relation to the BAMI case study. We found that common practices across many countries and cultures can be established by regulation and complied with at this defined standard level. However, the activities required to achieve such harmonization of practice, confront a quagmire of differences between practices in the clinics and countries participating in the standardization process, which have to be re-arranged or modified in order to fit. Cultural or local diversity-related issues faced by the BAMI teams include insurance practices, how the relationship and contact between patients and the clinical team are seen and managed, and how certainty about good communication can be reached in multilingual settings.

The language barrier and its importance was perceived differently especially in our mini-survey with BAMI teams to check their response to our findings after analysis of the data we had collected. All the responding study nurses regarded it as a major problem, i.e. they 'strongly agree' that language barriers hamper patient recruitment and therefore delay the trial. By contrast, for both the PIs and national co-ordinators it was not an important issue. These groups attribute the delay and recruitment issues to financial constraints and EU regulation.

> "[The] absence of commercial funding meant that all expertise had to be found in the university, e.g. statistics, regulatory [expertise]." (PI 2, UK)

This quotation from one senior clinician in BAMI sums up similar statements from several other clinician investigators. Others hinted that all problems in BAMI could have been solved easily if much more money had been available. In the specific context of BAMI with its small and closely interacting teams, this discrepancy in perception of problems between nurses and senior management staff was an unexpected finding. On the one hand, nursing staff perceived 'external' and cultural issues as requiring frequent decision-making and action, whereas senior clinicians, on the other hand, thought that money could readily solve such issues. The small sample size does not allow for a more detailed investigation of this point. Our interviews and observation provide only indications that the division of labour and tasks

between members of the trial teams and the subsequent differences in their experiences of problems confronted in trial conduct would form part of the explanation.

Attempts to support academic clinical trials in Europe

However, the problems from culturally diverse practices that have affected BAMI are likely to arise in other academic trials too. BAMI has been exceptionally exposed to issues arising from regulatory change to harmonize practice across Europe. The main reason is that the trial had been designed before the described changes in European ATIMP regulation were established. The new ATIMP regime came into force after the funding application for BAMI had been submitted and by the time BAMI started, it had to be fully complied with. BAMI is also the first Phase III multinational trial that sought and gained approval through VHP. One of the BAMI PIs explains this, citing the insurance issue as an example:

> "…this is an EU problem. The sponsor normally takes on the insurance responsibility, which we do, but each country has been told by their local [competent authority issuing ethical approval] that they have to get local insurance too. And again it's a real shame because the only people that are benefitting are the insurance companies. The study suffered because this is extra money that we didn't think we needed. I don't see how the patients benefit any more [from being] protected both ways. So, again, it's not particularly geared to facilitating this research. One could argue that, obviously, I have got a very cynical viewpoint because it has been so difficult. But it's simply that, you know, there's the information that we needed to plan for – it was just not available. We don't have an infrastructure that feeds into us. An industry would outsource the whole review to make sure they knew what was coming."' (PI 1, UK)

In order to support clinical teams in clinical trial research, when the problems they would encounter in the new regulatory set-up became apparent, The European Commission funded several long- and short-term projects to support pharmaceutical innovation. One of them was the AGORA project, led by University College London from 2013–2015. The acronym stands for ATMP GMP Open Access Research Alliance. AGORA aimed at addressing the problems academic research consortia encounter working effectively within the EU regulatory clinical trial framework. The vision was an institutional multinational academic platform in order to bundle and provide to other teams the information needed to run clinical trials in compliance with EU regulations and Directives across multiple country settings. The

AGORA[4] project organized several workshops and events to that effect. The account in their end of award report (AGORA 2016) captures the key problems BAMI faced, and potential solutions were envisaged:

> 'The aim of this project was to undertake a series of specific actions to address each of the current unmet needs and critical issues arising from our previous FP7 Academic Good Manufacturing Practice (GMP) study on the development and delivery of new advanced therapies for the treatment of cancers and regenerative medicine… . AGORA planned to create a resource to boost biomedical and clinical research through provision of a platform to facilitate consultation with biomedical researchers in the field. Recent EC actions have attempted to ensure the development, provision and free movement of ATMPs within the EU. However, FP7-funded research found substantial heterogeneity in the regulatory practice across member states which is leading to confusion and uncertainty and creating a severe barrier to development and delivery of these novel medicines which was weakening the position of EU academics and industry to collaborate and compete globally in this expanding field. The outcome of the current impact assessment by "Academic GMP" did not conclude that the current EU legislation needed revision but that a framework of support and training was needed to facilitate the implementation.'

However, AGORA explicitly aimed to foster phase-I and phase-II clinical trials in hospital environments to prepare the ground for industry sponsored phase-III trials. Being an academic phase-III trial, BAMI is one of the FP 7 projects that provide ample evidence of the need for infrastructure of the sort at which AGORA aimed. But BAMI itself could not find support there, not least because it started years before the platform was established. Concerning the future, it is also notable that the AGORA project ended in 2015 and it is an open question as to how long their informative website will remain accessible. In the autumn of 2016 its website *agora-gmp.org* contained a farewell letter, summarising its achievements.

5. Conclusion

Beyond the internal issues of the BAMI[5] multi-national clinical trial – including the quality and feasibility of the medical intervention, and the set-up and implementation of the trial

[4] AGORA stands for "**Advanced Therapy Medicinal Product Good Manufacturing Practice Open Access Research Alliance**".

following harmonized safety, security and ethics protocols – there are a range of external challenges to everyday practice which costs time and money to solve. Our findings give a detailed account of the complexity of conducting such a trial. They show that the clinical work is multifaceted and closely intertwined with 'external' cultural practices and conventions.

In the introduction to this article we set out to address three questions. They have been answered empirically in relation to the specific case, as we have shown how the common EU regulatory set up has affected trial conduct and which specific implications and unexpected challenges the national teams had to overcome in order to comply with both local expectations and EU standardized protocols. The third question, how cultural difference have affected BAMI as a clinical trial, has also been touched upon, but it will now be answered in more detail and serve as a starting point for our theoretical discussion of what the findings from this project may mean for the sociology of standardization.

A major practical accomplishment has been the adaptation to the local cultural rules in such a way that they achieve full compliance with harmonized regulations. For the sociology of standards and regulation this means that whilst harmonization demands creative solutions and financial support, it can often be achieved without substantial changes to cultural practices. Our findings respond to the challenge by Timmermans and Epstein (2010) to study in detail the effects of standards and regulations. Timmermans and Epstein's review is entitled "A World of Standards but not a Standard World" (2010). They argue that 'each standard achieves some small or large transformation of an existing social order' (p. 83) and that '"the specificity of the actual standard matters: Different standards will generate different outcomes for different users' (ibid.). 'Rather than making any totalizing claims about the nature or effects of these phenomena, we argue that their sociological import comes out most clearly through scholarship that is specific, empirical and located in concrete social settings' (p. 84).

Necessarily case-specific to regenerative medicine clinical trials, the findings should allow comparison between this new area of extensive and investment-heavy standard creation and

[5] An abbreviation for: 'The effect of intracoronary reinfusion of bone marrow-derived mononuclear cells (BM-MNC) on all-cause mortality in acute myocardial infarction'. BAMI is a Phase III clinical trial led by clinician scientists and funded by the European Commission's FP 7 Health programme.

findings from other areas of technical standardization. The specificity of the findings reported above allows us to make prominent points of wider sociological relevance. Firstly, the findings add substance to discussions on the implementation of the standards and show that the practices involved can be viewed and experienced differently by different practitioners depending on their professional role and wider social and regulatory environment. Secondly, it shows that practically applying new standards often confronts the practitioners with new insights into micro-level differences in practice that had seemed the same before, and it illustrates just how tightly specific ways of doing things are tied up and interwoven with multiple other conventional ways of doing things. Thirdly, and what appears at some level sociological common sense, changes required by new regulations are undertaken in such a way that they have as little impact on related and surrounding practices and expectations as possible.

Our findings infer that the field of clinical practice is sensitive to engrained values and beliefs about patient rights and good clinical practice that are touched by changes in everyday routines. At the same time, standardization as prerequisite to bringing new therapeutic techniques to a large patient population has become a key area of the current political economy in Europe. It may be helpful for scholars in the sociology of standards to consider those different aspects and compare findings in other studies according to these parameters to remain empirically specific, as Timmermans and Epstein demand, whilst sharing relevant dimensions for comparisons between findings from different areas of standardization.

To add more substance from our project to such a comparative discussion, we consider our findings regarding both the division of labour in the BAMI trial and its effects on how interviewees assess the new regulatory regime, and the investment dimension – again from the point of view of our subset of actors in regenerative medicine, who identify ambiguous effects of those standards on the field of regenerative medicine depending on the types of stem cells used.

BAMI team members in different roles evaluated the set of problems described differently. For example, there is a discrepancy between nurses and doctors in the day-to-day conduct of the trial, who rate cultural issues such as language as important problems, and the clinician scientist PIs, who predominantly see these cultural issues as minor problems affecting the

team mostly because of the financial constraints in publicly funded research. The NCCs[6] and trial nurses also reported that in industry-funded trials these problems would be solved centrally by the funder. The ways in which different BAMI actors perceived the challenges encountered, and ranked them in severity, also highlights the diversity of effect any standardization has on its different users. The discrepancy in evaluating the prominence of these problems highlights two key points for the wider debate on biomedical and technical regulations and their effects.

Firstly, whilst not facing the daily brunt of these issues, and thus at first glance seeming detached or even under-appreciative, the BAMI PIs' argument that most problems could be resolved with money has a science-policy dimension that needs to be pointed out clearly. According to them, expanding ATIMP (Advanced Therapy Investigative Medicinal Products) regulation to also cover treatments such as autologous adult stem cell therapies effectively disadvantages clinician-led research in regenerative medicine. The kind of stem cell therapy BAMI represents is seen as clinically promising by these experts (Mathur et al., 2017), but as unrewarding from an industry point of view. The procedure used in BAMI is not patentable and thus industry interest in developing and trialling it is lacking. BAMI has to make do with 6 million Euros awarded by the European Commission and no substantial additional industry support. Without the additional major costs arising from the streamlined regulation affecting BAMI, however, the cost-calculation that 6 million Euros would suffice to conduct this phase III clinical trial was credible when the funding application was put together in 2010.

The streamlining of all stem cell therapies under ATIMP on the one hand, which massively increases costs, and the lack of economic incentive for industrial sponsors to engage in autologous tissue repair research on the other, mean that the regulatory apparatus imposes an obstacle for this line of research. Money can overcome the issues BAMI faces – but in the public research sector this money is not available or offered. Thus, some of the PIs criticize recent European regulatory changes, because they see them as effectively influencing which stem cell research can go ahead, favouring particular forms of stem cell research over others without any scientifically or clinically valid reasons for that imbalance.

[6] NCC stands for National Coordinating Centre staff. In each country one hospital leads the trial in that country. The NCC recruits, contracts and assesses the work at other satellite hospitals that also recruit patients to BAMI.

Secondly, cultural differences are endemic and thus standardization always risks creating new sets of problems. While the frequent complications in day-to-day work and the financial limitations to solving problems have occasionally frustrated BAMI team members, they have highlighted to us as social scientists the intersection of different perceptions and routines that have evolved around patient autonomy, quality assurance and medical research. The cultural issues described indicate a web of culturally specific and embedded routine practices that involve a range of different institutions and contexts in which local clinical teams operate.

The harmonization standards that had to be complied with in BAMI have disrupted some threads in this web, and the teams struggle with how to repair the tears in the peculiar local fabric of interactions between insurance conventions, ethical expectation, patient autonomy and consent, and so on. The clinical staff in BAMI, NCCs especially, have learned a lot about the particularities of their own national systems of rules and cultural expectations, because they have had to align their practice with the harmonized rules for the whole multinational trial, and without industry experts who otherwise could take over the management of such issues. The experience may foster more independence from industrial sponsors and increase international collaborative spirit among clinical teams, if support infrastructures for academic biomedical sciences are built up – as was envisaged on a limited scale with AGORA[7].

Advancing regenerative medicine in Europe with academic research that pursues treatment routes that do not attract major industry sponsorship seems to require a much stronger support infrastructure. Our findings, combined with the existing problem descriptions from AGORA, suggest that a central institution would be needed, which bundles the varied and specialist expertise needed to implement a multinational trial accessible to publicly funded research-active cooperating clinical teams in Europe, providing services equivalent to those provided behind the scenes by industrial sponsors to clinical research teams. Currently, in phase III clinical trials, each team has to struggle through a maze of cultural and regulatory challenges. An accessible expert centre would provide a more level playing field between approaches to new therapies that promise better patient health without promising great financial rewards, and those that offer the latter too. It would also save resources, both monetary and motivational, for fostering a successful European clinical research community.

[7] AGORA stands for "**Advanced Therapy Medicinal Product Good Manufacturing Practice Open Access Research Alliance**".

Collectively our findings demonstrate the problems harmonization creates when new standardized rules must be brokered against varied and distinctive cultural expectations and institutional practices – many of which are outside the trial protocol but affect clinical routine actions on a daily basis.

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Bibliography

AGORA (2016) Final Report Summary AGORA, accessible online at Community Research and Development Information Service. <Source details>. Available at http://cordis.europa.eu/result/rcn/177747_en.html (accessed 18 June 2016).

Anele, D. I. O. (2006) Nigeria's Health Care Delivery System and Recent Biomedical Technologies: A Critical Survey in: Bender, W., Hauskeller, C., and Manzei, A., (Eds) *Crossing Borders Cultural, Religious, and Political Differences Concerning Stem Cell Research. A Global Approach,* pp. 207–224. (Muenster: Agenda Publishers).

Anderson, D. (2003) The patient recruitment market. An overview of today's issues. *Applied Clinical Trials*, 02 November 2003. <Source details>. Available at http://www.appliedclinicaltrialsonline.com/patient-recruitment-market (accessed 18 August 2016).

Baeyens, A. (2004) Impact of the European Clinical Trials Directive on academic clinical research, *Med Law,* 23, pp. 103–10.

Beltrame, L. (2014) The Therapeutic Promise of Pluripotency and its Political Use in the Italian Stem Cell Debate, *Science as Culture*, 23(4), 493-516.

Bender, W., Hauskeller C., Manzei, A. (Eds) (2005) *Crossing Borders: Cultural, Religious and Political Differences Concerning Stem Cell Research: A Global Approach*. (Muenster: Agenda Publishers).

Betancourt, J. R. and Jacobs, E. A. (1972) Language barriers to informed consent and confidentiality: the impact on women's health. *Journal of American Medical Women's Association*, [2000, 55(5), pp, 294–295].

Bowker, G. and Star, S. L. (1999) *Sorting Things Out*. (Cambridge, MA: MIT Press).

Cambrosio, A., Keating, P., Schlich, T. and Weisz, G. (2009) Biomedical conventions and regulatory objectivity: a few introductory remarks. *Social Studies of Science,* 39, pp. 651–664.

Campbell, D. T. and Stanley, J. C. (1963) Experimental and quasi-experimental designs for research in: Gage N. L. (Ed) *Handbook of Research on Teaching* (Chicago: Rand McNally).

Carr, E. C. J. and Worth, A. (2001) The use of the telephone interview for research. *Nursing Times Research,* 6(1), pp. 511–524.

Cartwright, N. (2007) Are RCTs the Gold Standard?, *BioSocieties,* 2, pp. 11–20.

Castel, P. (2009) What's behind a guideline? Authority, competition and collaboration in the French Oncology Sector, *Social Studies of Science,* 39, pp. 743–764.

Cressy, D. (2010) UK doctors demand research reform, *Nature News,* (17 May). doi:10.1038/news.2010.246.

European Commission (2001) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. *Official Journal of the European Communities* 1-5-2001, L 121/3M4.

European Commission (2002). Life Sciences and Biotechnology – a Strategy for Europe COM(2002)27. <Source details>. Available at http://ec.europa.eu/biotechnology/pdf/com2002-27_en.pdf (accessed 18 June 2016).

European Commission (2004) Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004. *Official Journal of the European Communities* 7-4-2004, L 102/48.

Epstein, S. (2007) *Inclusion: the politics of difference in medical research.* (Chicago: The University of Chicago Press).

European Commission and European Medicines Agency (2007) European Commission – European Medicines Agency Conference on the Operation of the Clinical Trials.

Faulkner, A., Geesink, I., Kent, J. and Fitzpatrick, D. (2008) Tissue-engineered technologies: scientific biomedicine, frames of risk and regulatory regime-building in Europe, *Science as Culture*, 17(2), pp. 195–222.

Gammelgaard, A., Rossel, P., Mortensen, O. S. et al. (2004a) Patients' perceptions of informed consent in acute myocardial infarction research: a questionnaire based survey of the consent process in the DANAMI-2 trial, *Heart,* 90, pp. 1124–1128.

Gammelgaard, A., Rossel, P., Mortensen, O. S. et al. (2004b) Patients' perceptions of informed consent in acute myocardial infarction research: a Danish study, *Social Science & Medicine,* 58, pp. 2313–2324.

Garattini, S. (European Commission) (2009) Can we facilitate multinational investigator-driven trials? <Source details>. Available at http://ec.europa.eu/health/files/clinicaltrials/docs/responses_2001-20/european_science_foundation_3.pdf (accessed 18 June 2016).

Hanna, P. (2012) Using internet technologies (such as Skype) as a research medium: a research note, *Qualitative Research*, 12(2), pp. 239–242.

Hartmann, M. (2012) Impact assessment of the European clinical trials directive: a longitudinal, prospective, observational study analysing patterns and trends in clinical drug trial applications submitted since 2001 to regulatory agencies in six EU countries, *Trials,* 13, pp. 53.

Hartmann, M. and Hartmann-Vareilles, F. (2006) The Clinical Trials Directive: how is it affecting Europe's noncommercial research, *PLoS Clinical Trials,* 1, p. e13.

Hauskeller, C. and Baur, N. (2017) Travelling Cells – Harmonized European Regulation and the BAMI Stem Cell Trial in: Van Pham, P. and Rosemann, A. (Eds) *Stem Cells in Clinical Application. Safety, Ethics and Regulation* (in press) (Springer)

Heads of Medicines Agency (HMA) (2010) Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications. <Source details>. Available at http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/invClinica/2010/docs/VHP-version-2_March-2010.pdf (accessed 18 June 2016).

Hogle, L. (2009) Pragmatic objectivity and the standardization of engineered tissues, *Social Studies of Science* 39, pp. 717–742.

Hollak, C. E. M., Biegstraten, M., Baumgartner, M. R. et al. (2016) Position statement on the role of healthcare professionals, patient organizations and industry in European Reference Networks, *Orphanet Journal of Rare Diseases*, 1: 1–11. <Source details>. Available at http://hdl.handle.net/11245/1.510979 (accessed 21 August 2016)

Holt, A. (2010) Using the telephone for narrative interviewing: a research note, *Qualitative Research*. 10(1), pp. 113–121.

Howard, D. and DeMets, D. (1981) How informed is informed consent?, *Controlled Clinical Trials*, 2, pp. 287–303.

Hunter, P. (2011) The health of European medical research, *European Molecular Biology Organization Reports*, 12, pp. 110–112.

Irvine, A., Drew, P., and Sainsbury, R. (2013) 'Am I not answering your questions properly?' Clarification, adequacy and responsiveness in semi-structured telephone and face-to-face interviews, *Qualitative Research*. 13(1), pp. 87–106.

Jasanoff, S. (2005) *Designs on Nature: Science and Democracy in Europe and the United States*, (Princeton: Princeton University Press).

Krafft, H. (2010) One voice for clinical trials in Europe, *Regulatory Rapporteur,* 7, pp. 21–24.

Krafft, H., Bélorgey, C. and Szalay, G. (2012) Experience and further development with the Voluntary Harmonisation Procedure for multinational clinical trials in the European Union, *Nature Reviews Drug Discovery*, 11, pp. 419–420.

Kucia, A. and Horowitz, J. (2000) Is informed consent to clinical trials an "upside selective" process in acute coronary syndromes?, *American Heart Journal*, 140, pp. 94–97.

Lampland M. and Star, S. L., (Eds) (2009) *Standards and Their Stories: How Quantifying, Classifying and Formalizing Practices Shape Everyday Life*. (Ithaca: Cornell University Press).

Lemaire, F. and Baeyens, A. (2002) Clinical research: a European Union directive, *Intensive Care Med*, 28, pp. 660.

Mathur, A., Aviles, F., Dimmeler, S., et al. (2017) The consensus of the Task Force of the European Society of Cardiology concerning the clinical investigation of the use of autologous adult stem cells for the treatment of Acute Myocardial Infarction and Heart Failure – update 2016, *European Heart Journal*, doi:10.1093/eurheartj/ehw640.

Nwobike, J. (2006) Pharmaceutical Corporations and access to drugs in developing countries: The way forward, 4 Sur *International Journal on Human Rights*, 3(4), pp.127–143.

Oates, J. (2015) Use of Skype in interviews: the impact of the medium in a study of mental health nurses, *Nurse Researcher*, 22(40), pp. 13–17.

Petryna, A. (2009) *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects*. (Princeton: Princeton University Press).

Rosemann, A. and Sleeboom-Faulkner, M. (2016) New regulation for clinical stem cell research in China: expected impact and challenges for implementation, *Regenerative Medicine*, 11(1), pp. 5–9.

Rothwell, P. (2005) Treating individuals. External validity of randomized controlled trials: 'To whom do the results of this trial apply?', *Lancet*, 365, pp. 82–93.

Salter, B. (2007) Bioethics and the global moral economy: the cultural politics of human embryonic stem cell science, *Science, Technology and Human Values*, 32(5), pp. 1–28.

Salter, B. and Salter, C. (2013) Bioethical ambition, political opportunity and the European governance of patenting: the case of human embryonic stem cell science, *Social Science and Medicine*, 98, pp. 286–292.

Salter, B., Zhou, Y. and Datta, S. (2014) Making Choices: Health Consumers, Markets and the Global Stem Cell Therapy Market, *BioDrugs*, 28, pp. 461–464.

Schenker, Y., Leo, B., et al., Navigating language barriers under difficult circumstances, *Annals of Internal Medicine*, 149(4), pp. 264–269.

Star, S. L. (1991) Power, technologies and the phenomenology of conventions: on being allergic to onions in: J. Law (Ed) *A Sociology of Monsters: Essays on Power, Technology and* Domination, pp. 26–56. (London: Routledge).

Star, S. L. (1995) The politics of formal representations: Wizards, gurus and organizational complexity, in: S. L. Star (Ed) *Ecologies of Knowledge: Work and Politics in Science and Technology,* pp. 88–118. (Albany: State University Press).

Stephens, N. (2007) Collecting data from elites and ultra elites: telephone and face-to-face interviews with macroeconomists, *Qualitative Research.* 7(20), 203–216.

Stephens, N., Lewis, J. and Atkinson. P. (2013) Closing the regulatory regress: GMP accreditation in stem cell laboratories, *Sociology of Health and Illness*, 35 (3), pp. 345–360

Sunder Rajan, K. (2010) The Experimental Machinery of Global Clinical Trials: Case Studies from India in: A. Ong and N. Chen (Eds) *Asian Biotech: Ethics and Communities of Fate* pp. 55–80. (Durham, Duke University Press).

Timmermans, S. and Epstein, S. (2010) A World of Standards but not a standard World: Toward a Sociology of Standards and Standardization, *Annual Review of Sociology*, 36, pp. 69–89.

Veerus, P., Lexchin, J. and Hemminki, E. (2014) Legislative regulation and ethical governance of medical research in different European Union countries, *Journal of Medical Ethics*, 40(6), pp. 409–413.

Waldby, C. and Salter, B. (2008). Global Governance in Human Embryonic Stem Cell Science: Standardization and Bioethics in Research and Patenting, *Studies in Ethics Law and Technology*, 2(1), pp. 1–23.

Weber, S., Wilson-Kovacs, D. and Hauskeller, C. (2010) The Regulation of Stem Cell Therapies: Comparing the UK and Germany, *Human Tissue Research* (Lenk, C. et al., eds.). (Oxford: Oxford University Press). pp. 159–167.

Will, C. (2007) The Alchemy of Clinical Trials, *BioSocieties*, 2, pp. 85–99.

Will, C. and Moreira, T. (2010) *Medical Proofs, Social Experiments. Clinical trials in shifting contexts*. (Farnham (UK) and Burlington (US): Ashgate).

Wilson-Kovacs, D., Weber, S. and Hauskeller, C. (2010) Stem Cells Clinical Trials for Cardiac Repair: Regulation as Practical Accomplishment, *Sociology of Health and Illness*, 32(1), pp. 89–105.