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Communication

Multi-country stem cell trials
The need for an international support structure

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Introduction

Regenerative stem cell research is now rapidly moving toward the clinic and routine medical applications. With the number of Phase II and III trials growing, the conduct of multi-country clinical research collaborations is becoming increasingly important. These partnerships accelerate processes of clinical translation, and form the basis for marketing approval of new therapies in multiple countries (Martell et al., 2010). At present, however, the conduct of international stem cell trials is hampered by a high level of regulatory heterogeneity across countries, and the absence of internationally harmonized governance frameworks (Bubela et al., 2014). Even though drug regulatory authorities in the USA, the European Union and Canada have now initiated collaborations that focus on the convergence of regulatory procedures for cellular therapy products, globally harmonized regulatory procedures are far-off (Arcidiacono et al., 2012). Japan for instance, has recently introduced a fast-track approval path for stem cell therapies (Cyranoski, 2013), and in China and India drug regulatory agencies have at present only issued provisional regulations and regulatory guidelines whose legal power is limited (Sleeboom-Faulkner and Patra, 2011; Viswanathan et al., 2013; Rosemann, 2013). But complications arise also from the ongoing growth of unregulated stem cell treatments that are offered to patients without systematic proof of safety and efficacy in many countries (Lysaght and Sipp, 2014; Ogbogu et al., 2013). Lucrative business opportunities and the existence of regulatory grey areas have given rise to uncontrolled applications and the emergence of transnational entrepreneurial networks that advocate alternative forms of research regulation. Professional associations such as the International Cellular Medicine Society (ICMS), for example, have developed their own guidelines and IRB and accreditation services (Blasimme, 2013). These activities support experimental for-profit interventions with stem cells outside of the methodological format of the randomized controlled trial and independent from the review procedures of drug regulatory agencies (Rosemann, under review). This diversification of clinical research standards within and across countries makes efforts of international harmonization increasingly difficult.

In Part I of this paper I will introduce four central challenges to the organization of international stem cell trials that emerge from this high level of regulatory variation. These obstacles apply in principle to all innovative multi-country stem cell trials that are subject to approval by a drug regulatory authority, including trials with (minimally manipulated) autologous stem cells. These challenges are especially pronounced, however, in the case of trials with pluripotent stem cells that involve increased technical complexity and higher risks for patients. Exceptions are trials that involve established stem cell treatments (such as the use of hematopoietic stem cells for leukemia), or studies that make use of autologous stem cells that are less than minimally manipulated and not subject to regulatory scrutiny (Li et al., 2014). Then in Part II I will argue for the need of an international support structure that systematically addresses these problems. In this regard, I will introduce five measures that may help to reduce existing difficulties and to conduct international stem cell trials in a more effective and cost-efficient way.

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Challenges to the organization of multi-country stem cell trials

A first challenge to the organization of multi-country stem cell trials is the necessity to conduct long-term in-depth research into the regulatory requirements of drug regulatory authorities in multiple countries (OECD, 2011). Stem cell therapies, as pointed out by Martell and colleagues 'do not neatly fit into current regulatory categories', and the barriers of translating stem cell-based approaches in functioning therapies lie 'in both technical and regulatory constraints' (Martell et al., 2010: 451). Regulations for the clinical use of stem cells are in many countries emerging only gradually and far-reaching regulatory differences exist. For clinical investigators and industry this diversified and rapidly changing situation is confusing and poses significant organizational difficulties (Rosemann, 2014a). What is required is a long-term, reflective engagement with the review and approval procedures that are handled by the drug regulatory authorities in the countries in which a trial is conducted. In order to develop study protocols that are compliant with the demands of multiple regulatory agencies, gaps between jurisdictional frameworks must be identified at an early stage of the clinical translation process. This is a difficult task that takes time and may be complicated by language barriers, insufficiently defined regulatory procedures, cultural differences and disparities in the enforcement of regulatory protocols (Ravinetto et al., 2013). It is complicated, furthermore, because the regulatory issues that are associated with the development of autologous stem cell therapies (Hourd et al. 2014) do in important respects differ from the characteristics that need to be taken into account in the context of clinical trials with pluripotent stem cells (Andrews et al., 2014).

A second challenge is that the interaction with medical authorities in multiple countries is resulting in a very high level of organizational complexity (Minisman et al., 2012). To file applications at multiple drug regulatory agencies is a time, cost and labor-intensive process that requires specially trained staff and a well-functioning administrative infrastructure (Rosemann, 2014b). While for industry-sponsored trials this is not necessarily a problem, for academic research groups and small-to-mid size biotech companies (which at present are the main sponsors of clinical stem cell trials) these resources are often not available and difficult to acquire (Keirstead, 2012).

A third type of challenge are time delays, increased costs and uncertainties that arise from non-existent or still emerging regulatory procedures in some countries. In China, for instance, where effective regulatory procedures for the clinical testing of stem cell-based therapeutic approaches have until 2012 been non-existent, the China Food and Drug Administration (CFDA) has repeatedly refused to accept incoming investigational new drug (IND) applications for stem cell-based products (Rosemann, 2013). Such unresolved regulatory issues can cause long-drawn-out delays and additional costs to the sponsors of clinical stem cell trials, and result in the need to apply for regulatory approval in another country where regulatory procedures are clearer, and to conduct the trial there (Bhagavati, 2014). But unresolved regulatory issues and the potential for sudden regulatory changes exist also in countries with highly developed regulatory frameworks. Noteworthy is, in particular, the ongoing debate on who should regulate autologous stem cell interventions (Zarzeczny et al., 2014). In the USA, for instance, think tanks are using the case of autologous stem cells in order to promote broader deregulation and several companies and professional societies (most prominently the ICMS) have argued that 'autologous cell products should be treated as part of medical practice and thus not subjected to marketing approval' (Bianco and Sipp, 2014). These calls have resulted in a bill for the Freedom of Choice Act that was put forward to the US congress in April 2014. According to this bill investigational stem cell technologies could be sold to terminally ill patients, outside of the control of the US Food and Drug Administration (FDA) (Morgan, 2014). Similar developments can also be reported from other highly regulated countries. Australia, for instance, has exempted autologous stem cells from the review procedures of its drug regulatory agency (Tuch and Wall, 2014) and in Italy the use of autologous mesenchymal stem cells has been taken out of the jurisdiction of the Italian Medicine's Agency in 2013 (Berger et al., 2014). These developments are likely to influence regulations in other countries (Bianco and Sipp, 2014). Most importantly, however, the jurisdictional variation in regulatory frameworks and the prospect of ongoing policy changes make the implementation of multi-country stem cell trials more difficult and increase the risk of organizational complications, unexpected or misplaced investments and time delays.

A fourth challenge is that the high level of regulatory variation across countries necessitates far-reaching forms of scientific self-governance, training and procedural adjustments in participating clinical trial sites (Rosemann, 2014b). A central reason for this is, that the existence of regulatory differences between national jurisdictions is reflected in contrasts of clinical research practices and methodologies, at the level of local medical institutions. In many countries, moreover, knowledge on the conduct of systematized controlled stem cells trials is often limited among clinical researchers (Li et al., 2014). These disparities between and also within local hospitals form a clear threat to the scientific integrity of international stem cell trials (OECD, 2011). As a result, intensive forms of staff training and adjustments of local clinical research practices are necessary, so that standardized research protocols can be implemented (Ravinetto et al., 2013). Standardization requires, furthermore, the implementation of reliable monitoring and control infrastructures. For academic investigators and small-to-mid size companies the performances of these tasks pose a significant organizational and financial burden (Keirstead, 2012). Unless sufficient funding for these forms of education and scientific self-governance is acquired, multi-center international stem cell trials cannot be conducted.

The need for an international support structure

The International Society of Stem Cell Research (ISSCR) has in 2010 called for the need to harmonize regulations for the clinical translation and commercialization of stem cell-based products and therapies (Martell et al., 2010). However, in 2014 the global regulatory landscape for clinical stem cell research remains as diverse as before. This situation continues to pose problems to the organization of transnational stem cell trials. What is needed in order to improve this situation is