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# **Stem Cell Clinical Trials**

**Achim Rosemann**

*Researcher for the ESRC Bionetworking in Asia project*

Throughout human history decisions on how to treat sick or disabled persons were almost always based on personal experience, and on the observation of individuals or small groups of patients. But, following severe medical accidents and dramatic cases of exploitative medical experiments, increasingly controlled and systematized forms of clinical research were institutionalized in regulation and law, and enforced by government agencies (Roman 2014). Since the late 1970s, the standard way of drug development has occurred through the translation of basic research discoveries from (1) the lab bench (basic research), to (2) experiments in animal models (pre-clinical research), to (3) the testing of a candidate therapy in the context of human clinical trials (clinical research) (Woolf 2008). The go-ahead for the leap from preclinical to human subject research, and subsequently, to routine use and marketization, is given by national-level drug regulatory agencies; government bodies (such as the US Food and Drug Administration, or the European Medicines Agency) that control and oversee the testing and marketization of new drugs through formalized investigational and review procedures (Eichler *et al.* 2010).

Since the results of a single clinical study are rarely considered as reliable evidence for the efficacy and safety of a medical product, device or therapy, an elaborate system of clinical trials emerged, *in which the clinical testing of new drugs is divided in four phases* (Friedberg, Furberg and DeMetz 2010). Phase I to III clinical trials test the safety and efficacy of a candidate therapy and are conducted in the context of an Investigational New Drug Application (IND) procedure, under the supervision of a drug regulatory agency. Phase IV trials are post-marketization trials. Phase I trials are first-in-human trials that are designed to test a drug's safety, toxicity and the most optimal dosage. They follow from systematic preclinical evidence and enroll relatively small numbers of patients (*ibid.*). Phase II trials test for the efficacy of a candidate therapy. They are conducted only once the safety of a new medicinal product or device has been successfully proven in a phase I human trial. In industry-sponsored compound-based drug trials, commonly between 200 and 600 human subjects are enrolled in phase II trials (*ibid.*). However, in stem cell clinical trials the number of patients is usually much smaller (Hyun 2013). The purpose of phase III trials is to confirm the efficacy of a candidate therapy in a larger cohort of patients. The therapeutic effects of a drug are, as a rule, compared with existing standard treatments, or placebo treatment. Phase III trials, can enroll between 500 and 20.000 patients (Friedberg, Furberg and DeMetz 2010). But again, in the context of stem cell clinical trials, or rare disease trials, this number can be smaller. If the safety and efficacy of a new medicinal medical product or device has been confirmed in phase I to III trials, drug regulatory authorities are authorized to give the go-ahead for routine use and marketization of a therapy (*ibid.*). The therapy is now legally available in the jurisdiction in which it has been licensed and approved. Phase IV trials are post-marketization studies. These trials evaluate the long-term

effects of an approved drug and its side effects, morbidity and also mortality. Such phase IV studies are commonly longitudinal studies that are conducted over several years (*ibid.*).

Since the 1980s, phase II and III trials are customarily conducted as *double-blinded randomized controlled clinical trial format*, which currently counts as the methodological gold standard (Timmermans and Berg 2004). Double blinding, randomization and the use of control groups, are procedures designed to minimize bias, i.e. factors that distort the factual nature of an observation or event (Friedberg, Furberg and DeMetz 2010). A control group is, in essence, a comparison group of human study subjects, who are not treated with the investigational agent (i.e. the tested medicinal product or device). These control groups are treated either with a placebo (a placebo-control group) or a different treatment (active comparator group) (*ibid.*). Surgery-based trials make occasionally also use of a control group where patients undergo a sham surgery (sham-controlled trials) (*ibid.*). If for ethical reasons the work with a placebo or sham-surgery control group is seen as unacceptable, the study is called an “open label trial” (i.e. both patients and researchers know which treatment is administered) (Sedgwick 2011). Randomization refers to the assigning of study participants to the investigational and control groups, based on an equal chance procedure. This means, the different groups of a trial become comparable, because it reduces selection bias, and ensures that biological covariates in patients, that may affect the treatment outcome, are equally distributed between treatment groups (Friedberg, Furberg and DeMetz 2010). The concept of blinding refers to a procedure that keeps patients, trial investigators and participant assessors (the persons who collect the data) unaware of whether patients are part of an intervention or a control group, so that the behavior of these groups (and in particular the response of patients) will not be affected by this knowledge (*ibid.*).

## **Clinical trials with stem cells**

Clinical stem cell trials are based on the same methodological procedures, as other forms of drug trials (Rosen 2006). There are, however, some central differences to clinical trials that test small-molecule and compound-based drug products.

A first difference is that the majority of stem cell trials are conducted either as academic (i.e. investigator-initiated) clinical trials, or as clinical trials where small-to-mid size biotech companies act as sponsor. Large-scale pharmaceutical companies have so far only invested in preclinical research with stem cells, and industry-sponsored trials have not yet been launched (Ichim, Riordan and Stroncek 2011).

A second difference is that stem cell trials usually make use of significantly smaller numbers of patients. Phase I trials do often include only between 10 and 40 patients. Phase II trials may enroll between 20 and 100 patients, and phase III trials between 120 and 500 patients. Reasons are the high costs of stem cell trials, the difficulty to recruit sufficient numbers of patients and the fact that many of the treatments that are treated with stem cells are relatively rare diseases, or orphan diseases (Hyun 2013).

A third difference relates to the specific biological characteristics of stem cells, which pose a number of risks and practical challenges to their use in clinical trials (*ibid.*). The most important of these features are:

- (1) **Heterogeneity / undesired differentiation:** The ability of stem cells to differentiate in a host environment in undesirable ways, which may cause injected cells to differentiate into teratoma and other tumorous cells (Hassan and El-Sheemy 2004).
- (2) **Mechanisms of action and migration:** The mechanism of action of stem cells that unfold upon injection in a human host environment, are frequently still unknown. Not only is there the risk of dysfunctional differentiation, but there is also the risk of cell migration into areas of the human body, where injected cells could cause more harm than good (Bianco *et al.* 2013).
- (3) **Microbiological contamination:** micro-biological interaction processes of stem cells in lab and hospital environments are complex, and form a potential source of pollution, that may affect the therapeutic efficacy and potency of stem cells, and result in the transmission of viruses or pollutants that may cause severe adverse effects in patients. Cell cultivation and manufacturing of clinical grade stem cells for transplantation requires, therefore, highly skilled staff and first good manufacturing practices (GMP) approved lab facilities in the both, manufacturing sites and clinics. These factors form a significant cost factor for clinical trials and subsequent routine applications (Cobo *et al.* 2007).
- (4) **Fragility:** the successful survival of stem cells requires highly controlled conditions, and a large numbers of transplanted cells die after injection. From a perspective of production and transportation stem cells are problematic, because they have a short shelf life, and even short-term variation in environment conditions may decrease the viability and biological characteristics of stem cells, which will influence their behavior and efficacy upon therapeutic injection (Franklin and Kaftantzi 2008).
- (5) **Donor variability:** Donor-to-donor variability is a further challenge for stem cell clinical trials. It causes different biological responses in patients, which may result not only in strong variation with regard to treatment efficacy, but also in different degrees of HLA rejection, and related symptoms (Siddappa *et al.* 2007).
- (6) **Risks related to surgery:** Since many stem cell treatments involve surgery based injection procedures, the full range of surgery-related medical risks apply to these stem cell trials. These risks are: bleeding, microbial contamination, meningitis, and in trials for neuro-surgical disorders such as stroke or spinal cord injury, also the loss of cognitive, sensory and motor function (Montgomery 2010; Raore 2011).

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