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Autologous bone marrow-derived stem cell therapy in heart disease: Discrepancies and contradictions

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ABSTRACT

Background: Autologous bone marrow stem cell therapy is the greatest advance in the treatment of heart disease for a generation according to pioneering reports. In response to an unanswered letter regarding one of the largest and most promising trials, we attempted to summarise the findings from the most innovative and prolific laboratory.

Method and results: Amongst 48 reports from the group, there appeared to be 5 actual clinical studies ("families" of reports).

Duplicate or overlapping reports were common, with contradictory experimental design, recruitment and results. Readers cannot always tell whether a study is randomised versus not, open-controlled or blinded placebo-controlled, or lacking a control group. There were conflicts in recruitment dates, criteria, sample sizes, million-fold differences in cell counts, sex reclassification, fractional numbers of patients and conflation of competitors' studies with authors' own.

Contradictory results were also common. These included arithmetical miscalculations, statistical errors, suppression of significant changes, exaggerated description of own findings, possible silent patient deletions, fractional numbers of coronary arteries, identical results with contradictory sample sizes, contradictory results with identical sample sizes, misrepresented survival graphs and a patient with a negative NYHA class.

We tabulate over 200 discrepancies amongst the reports. The 5 family-flagship papers (Strauer 2002, STAR, IACT, ABCD, BALANCE) have had 2665 citations.

Of these, 291 citations were to the pivotal STAR or IACT-JACC papers, but 97% of their eligible citing papers did not mention any discrepancies. Five meta-analyses or systematic reviews covered these studies, but none described any discrepancies and all resolved uncertainties by undisclosed methods, in mutually contradictory ways. Meta-analysts disagreed whether some studies were randomised or "accepter-versus-rejecter". Our experience of presenting the discrepancies to journals is that readers may remain unaware of such problems.

Conclusions: Modern reporting of clinical research can still be imperfect. The scientific literature absorbs such reports largely uncritically. Even meta-analyses seem to resolve contradictions haphazardly. Discrepancies communicated to journals are not guaranteed to reach the scientific community.

Journals could consider prioritising systematic reporting of queries even if seemingly minor, and establishing a policy of "habeas data".

1. Introduction

"Oh! what a tangled web we weave …".

Walter Scott [1].

Extraordinary claims require extraordinary evidence. Exciting advances from a number of groups now report the ability to repair the human myocardium with stem cells from the bone marrow of the same patient. Meta-analytic synthesis is a crucial step for clinicians to assess the safety and consistency of the bone marrow stem cell effect. It may seem a much easier task to undertake a meta-analysis [2,3] than conduct primary research [4,5]. In reality it can be just as difficult in meta-analysis as in primary research to ensure correct recording of raw data: the study reports themselves.

One challenge we faced when examining papers from the foremost group in this field was discrepant information, which we defined as pairs of statements that could not both be true [6]. One very prominent, highly regarded and widely-cited cluster of reports proved particularly challenging despite being conducted in time of clear standards for reporting of clinical studies [7]. Enquiry to the authors and responsible institutions directly, and separately via the journal [8], did not yield clarifications.

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Table 1
Design discrepancies.

Discrepancy ID	Discrepancy	Publication 1[a]	Publication 1 detail	Publication 2[a]	Publication 2 detail	Publication 3[a]	Publication 3 detail	Publication 4[a]	Publication 4 detail
ICARUS-101	Including/excluding the index case	Circ 2002 (32)	Case report done first, and then "To confirm these results and validate this promising new therapy for MI, we established a clinical trial involving 20 patients"	Autol Tis Eng (33)	Case report patient, 30 March 2001 was "the first in a larger phase I clinical trial"	Cell Prolif (23)	Table 1 makes clear that Case report patient was separate from the trial of 20	Remodelling (34)	(Same author as Chapter) states 1 + 10 = 11 patients with AMI have been treated
ICARUS-102	Autologous or allogeneic? Between 99 and 724 patient "stem cell deficit", who presumably received allogeneic?	STAR (6)	All completed 5 year invasive follow-up by 11 Feb 2010 i.e. all 191 received stem cells by 10 Feb 2005	BALANCE-JACC (27)	62 patients with Acute MI received stem cells by end of 2003	Adjuvant (36)	120 patients were treated and 120 patients were controls. Four groups (of 30) received (i) stem cells, (ii) stem cells plus dobutamine, (iii) stem cells, dobutamine and dipyridamole or (iv) stem cells, dobutamine, dipyridamole and macroalbumin aggregates.	SEPAX (35)	(p207) At least 28% × 53 = 15 peripheral arterial disease patients, and 4% × 53 = 2 DCM patients received manually processed cells
ICARUS-102 (cont.)		SEPAX (35)	By Nov 2006, only 217 bone marrow aspirates had been processed, but between 316 and 941 patients have received cells (see Table 8 for balance sheet)						
BS-101	Randomised or accepter–rejecter	BEST (9)	Definitely randomised between cell therapy and control, e.g. pages 53, 67	STAR (6)	"Patients refusing cell therapy acted as the control group", p723	P1665 (20)	Same document describes it both as randomised and non-randomised		
BS-102	Placebo (i.e. blinded) or open control	BEST (9)	Describes randomization, but not the use of placebo	STAR (6)	Describes a controlled accepter rejecter study. No placebo mentioned	Curr Op (37)	BMCs vs. Placebo		
BS-103	Overnight cultivation of cells	STAR (6)	No	BEST (9)	Yes (publications' references [6,8])	P1665 (20)	Yes		
IACT-101	Existence of a control group	SCHLÜSSEL (11), IACT-Cardiovisionen (16)	No, no	IACT-JACC (12), IACT-Nature CPC (13)	Yes (1:1), yes (1:1)	IACT-Regeneration (15), P549 Acute Cardiac Care (18)	Yes (non 1:1), yes (non 1:1)	P1408 (19)	Yes
IACT-102	Accepter–rejecter (3 publications by group)	IACT-JACC (12)	Accepters versus rejecters	IACT-Nature CPC (13)	Accepters versus rejecters	IACT-Neuter (21)	Same document describes it both as randomised and non-randomised		
IACT-102 (cont.)	… versus Randomised (7 publications by same group regarding	TED (author's response to (61))	RANDOMISED: "all our chronic patients (n = 36) (the IACT study) fulfilled the same inclusion criteria (e.g. randomization…)"	FIVE (22)	Table 1: states IACT is: "RANDOMISIERTE, kontrollierte Studie"	IACT-Regeneration (15)	In the RANDOMISED control group no significant changes were observed…	Cell Prolif (23)	RANDOMISED Study