Manipulating patients in clinical trials: two case studies

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Practising quaternary prevention – namely, ensuring not to harm the patient – is here presented in two clinical trials. Two patients were manipulated by the same cardiology service on two research instances: one for a pharmaceutical treatment, the other for an invasive treatment. Patients were then asked to tell about their experience during a general practice encounter. Both patients have approved these versions of their testimonials, understand their importance, and agreed to their dissemination.

Letter from a general practitioner to the president of the ethics committee, Hospital N, Charleroi (extract)

[……..]

This 52 year-old patient who'd had a bypass surgery, an angioplasty and two stents comes to me on a visit with a few papers coming from a clinical study called "*Global Leaders*," dealing with a medication that they were told was "new."

They signed a consent form for a double-blind, phase IV study (Ticagrelor vs. Clopidrogel) on which it was written that the signatory authorized the research them to inform their general practitioner about the study.

The consent form also mentioned that the study was approved by an ethics board. The name of the committee was not mentioned in the documents they had received.

Ticagrelor is a well-established product and its performance against Clopidrogel's is much debated.

The patient trusted his cardiologist, who was not in charge of the study and he don't know the name of the researcher.

I was not made aware of this particular study.

This product is not new. It was discussed in the *New England Journal of Medicine* in 2009 and by the *Haute Autorité de Santé* in 2011. Results showed that it could be slightly better than Clopidrogel but *Prescrire* (2011, 333: 488-493) does not recommend it as it does not significantly improve the current treatment.

My patient was deceived, as they were told that it was a new medication and that their general practitioner would be informed.
This was a phase IV study that aimed at marketing and distributing the product in Belgium.

The patient is therefore used as a means for profit, which could have been acceptable, had it been aware of it. He believes in a scientific study but it is actually a marketing study which he doesn't know.

[……..]

All registered protocols should have an obvious purpose: the principle of beneficence. Forgetting this purpose is sloppy: risks for the patient appear greater than the anticipated benefits as "existing treatments" which have been proven effective exist… In regards to patient autonomy and informed consent (we all know that such consent is always somewhat directed, even in the best cases!) we can doubt of their true existence in this instance. Inter-collaborative processes can only take place when all details are available… which is not the case here.
(Commentary from a GP specialized in ethics)

A story about stem cells

At the beginning of 2013, a patient comes to me and asks for my advice whether he should participate in a clinical study. He was not that young anymore, yet his heart was much older than him. He was a smoker and was polymedicated since he'd experienced cardiac ischemia and an episode of atrial flutter.
I was not contacted by the cardiologists who were in charge of the study.
The study dealt with heart-decompensated patients. They would be forcing bone marrow stem cells to differentiate into cardiac cells before re-implanting them back into his heart.
I was a bit taken aback and contacted the cardiologists who were in charge of the study at our regional research hospital. I got a strange reply by e-mail from one of the investigators:
"*Following our phone conversation this morning, you will find the details of the study attached this e-mail. Complete protocols are kept by the investigators and thus cannot be shared with third parties.*"
The documents which could be communicated were the explicatory files and consent form given to the participants.
On the consent form was the certification *EudraCT 2011-001117-13* alongside the name of the financing body. It was *Cardio3 Biosciences*, a Belgian company (1). The study was therefore registered on *EU Clinical Trials Register* (2) and preliminary results had been published (3). To my request, the principal investigator made the full protocol available.
I was shocked with harsh and numerous inclusion criteria. Among many, patients required an ejection fraction equal or less than 30% and needed to use strict contraceptive methods.
My patient's cardiologist (who was not in charge of the study) reported the latest ejection fraction to be of 32%.
My patient was therefore not eligible. Furthermore, he was not aware of the contraceptive methods he needed to take. I told him this was dubious. That hiding to me – or omitting to share with me – some of the study details, and that the latest ejection fraction had not been considered, altered the credibility of the study.
We decided together that he would not participate in the study. Six months later, he could climb three flights of stairs without any exhaustion.

According to the Journal Les *Echos*, *Cardio3 Biosciences* (the funding body of this study) is listed with *NYSE Euronext Brussels* as well as *Euronext Paris* under the symbol CARD.
The same article establishes links between the research team and this industry through stock ownership. (4)
Venture capital firms invest in high-tech research. Such research can be promising and should be maintained.
However, nothing can excuse manipulation, omissions, imprecisions and conflicts of interest which will negatively impact the validity of the results.
Our patients are not cattle. They have a right to information and respect. It is our duty to advocate on their behalf, to understand what is at stake and to highlight the challenges of such research to inform and guide them.

Sources

(1) Cardio3 Bioscience http://www.c3bs.com/fr
(2) EU clinical trial register. Efficacy and Safety of Bone Marrow-Derived Mesenchymal Cardiopoietic Cells (C3BS-CQR-1) for the Treatment of Chronic Advanced Ischemic Heart Failure. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-001117-13
(3) Bartunek J, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, ElNakadi B, Banovic M, Beleslin B, Vrolix M, Legrand V, Vrints C, Vanoverschelde JL, Crespo-Diaz R, Homsy C, Tendera M, Waldman S, Wijns W, Terzic A. Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics.J Am Coll Cardiol. 2013 Jun 11;61(23):2329-38.
(4) Vandriesche L. Cardio3 Biosciences: des tests mis en cause. Journal L'Echo. 8 Juillet 2013 http://www.lecho.be/actualite/entreprises_pharma/Cardio3_Biosciences_des_tests_mis_en_cause.9372507-3003.art?ckc=1

General practitioners are seldom seen as potential collaborators in clinical research. However, they are in an ideal position to inform their patients – as long as they are perceived as partners and able to use the information provided. Mediating between medical technology and the patients, general practitioners are potential safeguards against practice-changing science that is sometimes dangerous. Being able to handle information technology and developing a sense of ethics should be at the heart of medical teaching.