LESSONS LEARNED REPORT

HTA Reference	14/45/04
Title	Chondroitin Sulphate for Hand Osteoarthritis: A Randomised, Placebo-Controlled Trial in Primary Care - the FACTUAL Study
Brief Title	The FACTUAL Study
Call	14/45 Chondroitin sulphate for people with hand osteoarthritis to improve hand function and pain
Sponsor	Keele University
Sponsors reference number	RG-0004-16-IPCHS
Host Organisation CTU	North Staffordshire Clinical Commissioning Group Keele CTU (UKCRC registration number: 36)
Trial Registration	EudraCT number: 2016-004670-18 [15 Nov 2016] ISRCTN: ISRCTN44644781 [18 Nov 2016] IRAS Number: 217828
Chief Investigator	Prof. Christian Mallen
Design	Investigator-, practitioner- and participant-blinded, parallel-group, placebo-controlled, randomised, superiority trial with internal pilot
Primary Objective	To determine the clinical effectiveness, cost effectiveness, and structure modifying effects of a package of 1200mg highly purified chondroitin sulphate and usual care compared with placebo chondroitin sulphate and usual care
Study Product, Dose, Route, Regimen	Highly purified chondroitin sulphate (Condrosan®, Bioiberica), 1200mg (3x 400mg capsules) daily, oral, taken once per day; plus usual care
Duration of administration	24 months
Comparator	Placebo chondroitin sulphate, 1200mg (3x 400mg capsules) daily, oral, taken once per day; plus usual care
Number of participants	380
Proposed start date	1 December 2015
Proposed end date	30 April 2020
Study Duration	53 months
HTA Programme Manager	Sue Pargeter
Closedown date	30 September 2017

This report was drafted by Professor George Peat (Academic Principal Investigator for the FACTUAL trial) with contributions from Clare Stevenson (Solicitor and Head of Academic Contracts, Keele University), Clark Crawford (Head of Research Integrity), and Kris Clarkson (Deputy Director, Keele CTU), and Professor Krysia Dziedzic (Head of Impact Accelerator Unit and Co-Investigator). The report was approved by Professor Christian Mallen (Chief Investigator) and Professor Elaine Hay (Director of the Research Institute for Primary Care & Health Sciences, Keele University). A copy of the report has been forwarded to Professor David Amigoni (Pro-Vice Chancellor, Research and Enterprise, Keele University), Professor Nadine Foster (Director, Keele CTU), Irena Zwierska (Research Development Manager), and Professor Karen Walker-Bone (Chair of the FACTUAL Trial Steering Committee).

Disclaimer

EXECUTIVE SUMMARY

The FACTUAL trial was to be the first trial in the UK (FTUK) of highly-purified, prescription-only chondroitin sulphate for hand osteoarthritis – licensed for this indication in several European countries but not the UK. A multidisciplinary research team led by academic researchers based at the Research Institute for Primary Care & Health Sciences at Keele University with co-applicants from Oxford, Leeds, and Nottingham University was awarded funding in open national competition through a commissioned call issued by the NIHR Health Technology Assessment (HTA). Bioibérica was the approved Marketing Authorisation Holder (MAH) for chondroitin sulphate, the active pharmaceutical ingredient (API) for Condrosan®, the Investigational Medicinal Product (IMP) to be used in FACTUAL. The API is the chemical reference substance in the European Pharmacopeia and had been selected for the previous NIH-funded GAIT trial in knee osteoarthritis. Bioiberica had agreed to donate all IMP and placebo for FACTUAL and to perform all labelling before shipping to UK.

A fully specified protocol and all patient-facing documentation and database modules were developed. Communication between parties was strong and the trial had experienced, critical and supportive independent oversight. Delays were identified early on in the timeline needed to negotiate and properly specify the contracting arrangements around IMP/placebo manufacture, supply, distribution, and storage for FACTUAL (just under 1 million capsules to be manufactured and labelled in Spain and shipped to a UK storage facility). However, the trial ultimately foundered on the inability to broker an agreement that was acceptable to both the funder and Bioiberica for sharing with Bioiberica the anonymised individual patient-level data upon completion of FACTUAL. This is despite an exhaustive search for a solution and Keele CTU being one of the few CTUs in the country to have an established 'controlled access' policy for data sharing. The trial was closed on 30 September 2017, 22 months after its official start date and without patient recruitment having begun.

Data sharing policy for publicly-funded clinical trials continues to evolve rapidly. Important lessons from FACTUAL include:

- The need for greater transparency in policies, contracts, and expectations on data sharing prior to the award of grant funding.
- There is a need to reconcile the funder's policy of seeking return on investment linked to data sharing with industry and current and emerging guidance to researchers that argues that "consideration of access requests should not in principle be influenced by whether the proposed secondary reuse is associated with a potential commercial benefit, directly or indirectly, in the short or the long term"[1] and which highlights the difficulties in differentiating commercial from non-commercial uses.
- The recognition that HEIs may be obliged as public bodies to release data under Freedom of Information requests.[2] While exemptions clearly do exist for release of data we feel the sector would benefit from clear advice from the funder when managing the conditions and expectations of the funder alongside the obligations of the Information Commissioner's Office.
- Greater clarity is needed on the role of the funder in the stewardship of data arising from trials funded by them.
- The particular circumstances of FACTUAL demanded earlier and more intensive risk assessment drawing on a wide range of expertise and shared across the Chief Investigator, the research team, Sponsor, and CTU. FACTUAL has contributed to the strengthening of a wide range of processes, Standard Operating Procedures and appointments at an institutional level. RaISE (Research and Innovation Support Enhancement) now means that there are professional research support teams in place to help ensure a more integrated and streamlined process whereby issues, including those around contracts, are considered from an earlier stage.

[1] Ohmann C, et al. Sharing and reuse of individual participant data from clinical trials: principles and recommendations. BMJ Open. 2017;7(12):e018647.

[2] Courts and Tribunals Judiciary, 2016. Available at: http://informationrights.decisions.tribunals.gov.uk/DBFiles/Decision/i1854/Queen%20Mary%20University%20of%20London%20EA-2015-0269%20(12-8-16).PDF

- There is a tension between the design of pragmatic trials of effectiveness for the NHS and current regulatory guidelines for efficacy trials of clinical interventions in osteoarthritis, and this may impact on industry engagement in the former.

BACKGROUND

The FACTUAL trial – which was to be the first trial in the UK (FTUK) for highly-purified, prescription-only chondroitin sulphate for hand osteoarthritis - was awarded funding in open national competition through a commissioned call issued by the NIHR Health Technology Assessment (HTA). The multidisciplinary research team was led by academic researchers based at the Research Institute for Primary Care & Health Sciences at Keele University with co-applicants from Oxford, Leeds, and Nottingham University. The trial built on Keele CTU's strong track record in delivering high-quality pragmatic clinical trials in primary care and the team's considerable knowledge of hand osteoarthritis. The team included an experienced PPIE co-applicant with hand OA and a dedicated and engagement Research User Group.

The Investigational Medicinal Product (IMP) chosen for FACTUAL was Condrosan®. Bioibérica is the approved Marketing Authorisation Holder (MAH) for chondroitin sulphate, the active pharmaceutical ingredient (API) for Condrosan® and several other medicinal products licensed for use in several European countries, but not currently the UK. The API is the chemical reference substance in the European Pharmacopeia and had been selected for the previous NIH-funded GAIT trial in knee osteoarthritis. Condrosan® is one such medicinal product containing the API and has the therapeutic indication of symptomatic treatment of OA. It is a prescription drug licensed in an EEA member state (Spain) since 2002. The FACTUAL trial was to be carried out under a Clinical Trial Authorisation (CTA) as a Type A CTIMP with Condrosan® being used within its therapeutic indication. Following meetings and correspondence between members of the research team and Bioibérica, Bioibérica had agreed to donate IMP and also manufacture and supply of the matched placebo (estimated 907,200 capsules in total) for FACTUAL and, from the outset, had stated their wish to have access to the de-identified individual patient-level data from FACTUAL for commercial and research purposes (e.g. as part of a registration dossier to seek a license for Condrosan® in the UK if findings were favourable). Bioibérica subsequently also agreed to label IMP and placebo prior to shipping to a third-party storage facility in the UK.

Delays needed to negotiate and properly specify the contracting arrangements around IMP/placebo manufacture, supply, distribution, and storage for FACTUAL were recognised early and discussed with the Programme Manager in December 2015 at which time a 6-month delay to trial recruitment was anticipated. While trial set-up activities continued according to plan, the process of specifying and agreeing a Manufacturing Contract with Bioibérica met with further delays. We reached an impasse with the Data Sharing Arrangements in the Manufacturing Agreement with the funder seeking the insertion of a clause requiring a negotiated return on investment prior to any release of individual patient-level data for commercial applications: a position that was unacceptable to Bioibérica given their stated intentions from the outset and the level of investment (estimated at between £200,000-350,000) and risk they were prepared to bear upfront for FACTUAL trial supply. On 23 March 2017, after repeated attempts to reach a Data Sharing Arrangements for commercial applications that was acceptable to both Bioibérica and the funder, the HTA Director requested that the trial be put on hold and payments suspended whilst negotiations continued (but also clarifying that the funder's position was not flexible). The existence of the PICASSO trial - a placebo-controlled trial of combined chondroitin sulphate/glucosamine hydrochloride for hand OA that was registered by Bioiberica on 1 July 2016 was flagged and a response from the research team justifying the continued need for FACTUAL was submitted to the Board Chair. A drop dead date of 30 June 2017 was set with the following objectives:

1. Signed data sharing agreements
2. A manufacturing slot secured for autumn
3. A firm timetable to start recruitment by 1 March 2018

The failure to satisfactorily resolve 1. and 2., and being unable to establish the feasibility of purchasing the clinical trial supply from Bioiberica led to the funder's decision on 6 July 2017 to close down the FACTUAL trial. The FACTUAL trial was closed down on 30 September 2017 prior to patient recruitment.

POSITIVE CONTRIBUTIONS AND OUTPUTS

The failure of FACTUAL was a major disappointment to all those involved in it, particularly the research team members who had worked extremely hard on the trial and the patients and members of the public who had played such an active role in a project that they were strongly in favour of. Despite its failure, it did highlight processes that worked well, produced some tangible outputs that will benefit future research, as well as being a catalyst for strengthening areas of trial design, delivery, and governance needed for low-risk CTIMPs at Keele.

Several communication channels worked well: there was timely and consistent access by the research team to the Sponsor, in particular their legal representative for advice and practical input over contracting arrangements; we maintained regular communication with the Programme Manager; we kept regular contact with the industry partner through scheduled teleconferences, face-to-face meetings, and emails. Regrettably the failure of the trial happened in spite of this.

PPIE was strong, with a core group of patients and members of the public convening to produce short videos on the nature of hand osteoarthritis, its impact, and current treatment options[3]. They were also heavily involved in the development of the FACTUAL study website, including an excellent list of Frequently Asked Questions (and answers) designed to support people considering joining the trial as well as those participants in the trial. A separate working group developed a short patient information document on hand osteoarthritis – the need for which had been recognised by Arthritis Research UK too. These tangible resources are available for dissemination, re-use in future studies and patient education. Similarly, the trial protocol and database modules developed for FACTUAL are being adapted for use in Keele CTU for other current and future trials.

Both Sponsor and CTU structures and processes were already evolving when FACTUAL was funded but it undoubtedly contributed to this process by providing concrete examples of gaps in Standard Operating Procedures for CTIMPs, key skills and knowledge that required strengthening, and where the roles and responsibilities of members of the research team needed clarification. Some of these are alluded to again below.

We are under no illusions that FACTUAL was, and would have been, a challenging trial to deliver. However, the trial ultimately foundered on the inability to broker a data sharing arrangement, an area of rapidly evolving policy and practice. The following section provide some additional detail on those lessons learned.

LESSONS LEARNED AND FUTURE AREAS FOR DEVELOPMENT

Data Sharing Policies in the Context of Industry Users/Collaborators Intending Commercial Applications

FACTUAL exposed major weaknesses in this area. At the time of starting FACTUAL, Keele was one of only 5 CTUs in the UK known to have an established data sharing policy.[4] Our Reviewed Access model (sometimes also referred to as 'controlled access') is regarded as the most suitable model for sharing data from publicly funded trials in the UK[5] and has worked well for previous data requests from other researchers employed in the public sector nationally and internationally. We had already drafted a data sharing plan in the FACTUAL

[3] Osteoarthritis of the hand. Available at: https://drive.google.com/file/d/0B8xFXyNSuPhwVW5QelU1VkM2MHM/view

[4] Hopkins C, et al. UK publicly funded Clinical Trials Units supported a controlled access approach to share individual participant data but highlighted concerns. *J Clin Epidemiol.* 2016;70:17-25.

[5] Tudur Smith C, et al. How should individual participant data (IPD) from publicly funded clinical trials be shared? *BMC Med.* 2015 Dec 17;13:298.

protocol – something that will be a required from 2019.[6] What was new in FACTUAL, and what is not covered explicitly in any of the current guidance, was that the request for anonymised data came from industry researchers, specifically from an industry partner that was donating IMP, placebo, and labelling to the trial, and that one of the purposes for the data request was regulatory, i.e. to support future applications to license Condrosan (and other chondroitin sulphate preparations) in the UK and in other countries. Our existing data request form was rejected by Bioiberica as inadequate for this purpose. Instead they required more formal Data Sharing Arrangements within the Manufacturing Agreement. We requested support from the funder via the Programme Manager but were told that the HTA had no templates to offer and that our best course of action was to generate a version and submit it to the funder for comment. From Bioiberica we obtained the Data Sharing Agreement used in their previous NIH-funded GAIT trial and adapted this for inclusion as Schedule 4 in the Manufacturing Agreement. However, the proposed use of FACTUAL trial data by Bioiberica for regulatory purposes was unacceptable to the funder unless a clause could be inserted which would provide for a negotiation prior to any release of data and aimed at securing a return on investment for the funder (e.g. through profit-sharing or cost reduction for NHS if a future licensing application in the UK was successful). This was unacceptable to Bioiberica who argued they were investing upfront in a trial whose outcome was uncertain (and might therefore be of no commercial value). There was also the perverse situation by which one of Bioiberica's competitors could request the FACTUAL trial data without incurring such a cost. Over the following months we attempted, through a long series of bilateral meetings and discussions, to persuade Bioiberica to drop their interest in regulatory use of the data (they would not), to persuade the funder to drop their insistence on the return on investment clause (they would not), to try to negotiate the upper limit of this negotiation to take account of Bioiberica's investment (some movement was made but not to where both parties could agree), and to persuade representatives from Bioiberica and the funder to discuss this directly with each other (which the funder refused). No further progress being made, the trial was closed.

Lessons learnt: (1) CIs and other key staff in the CTU and Sponsor must be aware of the potential issues in sharing data with industry partners. (2) Until further changes, it will be best to avoid arrangements that involve entering into trial arrangements that involve the explicit or implicit exchange of anonymised trial data for industry support or donation of services and products. (3) Keele CTU data sharing policies must be updated to cover data requests made from researchers based in industry. The recent ICMJE and CORBEL recommendations may be useful sources. (4) The funder's position which reserves the right to negotiate a return on investment from publicly funded, publicly sponsored trials with industry involvement and/or potential benefit needs to be made very clear to all applicants in the grant application process and at the point at which industry partners are engaged by the research team. Specifically the clause that the funder proposes to be used in such Data Sharing Agreements should be made explicit in the contract. (5) Some further clarification is needed on the role of the funder in data stewardship and the sustainable financial underpinning of the creation and management of data repositories arising from HTA-funded trials. (6) We also note the obligation upon HEIs as public bodies to release data under Freedom of Information requests, indeed Queen Mary University London has recently defended (unsuccessfully) a request for release of anonymous patient level data on one of the trials it sponsors. While exemptions clearly do exist for release of data we feel the sector would benefit from clear advice from the funder when managing the conditions and expectations of the funder alongside the obligations of the Information Commissioner's Office.

The following points are secondary matters which, although not the cause of the failure of the trial, nonetheless represent areas where we have learned important lessons for future studies:

Clinical Trials Supplies and Contracting for CTIMPs; CTIMP Pharmacy Support

Although classed as a Type A CTIMP, several aspects of FACTUAL were novel for Keele CTU: (i) First Trial in UK - IMP unlicensed in UK, (ii) large volume of IMP and placebo supply needed for the size and duration of FACTUAL and associated storage requirements (~1 million capsules), (iii) manufacturer based in EEA member state not UK. A large team, including identifying new individuals with specialist knowledge in some key areas,

[6] Taichman DB, et al. Data Sharing Statements for Clinical Trials - A Requirement of the International Committee of Medical Journal Editors. *N Engl J Med.* 2017 Jun 8;376(23):2277-2279.

was needed to deliver the trial. Co-applicants with CTIMP experience were included and a number of key individuals were identified or appointed after grant award but ideally would have been in place and accessible to contribute to the design, costing, and risk assessment as part of the funding application. Even with this, we would not have prevented the Data Sharing problem that was the reason for the failure of the trial.
Unusually for a manufacturer Bioiberica did not supply their own terms and conditions for the manufacture, supply, labelling and shipment of IMP and placebo. A considerable amount of time was therefore spent by the Sponsor's legal representative and members of the research team in drafting these.
Lessons learned: (1) Under the process of applying for Sponsorship prior to grant funding application, the risk assessment process for Keele CTU has been significantly strengthened in light of the experiences from FACTUAL and all CI/PI are made fully aware of these new requirements and offered training and support in relation to them. (2) A Clinical Trial Think Tank now convenes regularly to provide timely, critical review of all proposed trials. (3) Re-organisation of the Sponsor functions, research support on an Institutional level, and Keele CTU, including actively strengthening its pharmacy advisory team for CTIMPs, has been undertaken. For example, the new Research AiSE (4) Failure of an industry partner to supply its terms and conditions should be recognised as a red flag. An understanding that industry partners will need to supply their terms and conditions should be established early, when there may be the opportunity to seek an alternative supplier.

Identifying imminent relevant trials and ongoing active searching for newly registered relevant trials.
On 6 July 2016, approximately 22 months after first sharing the outline bid for our FACTUAL trial with Bioiberica, and 7 months after the FACTUAL grant award start date, Bioiberica registered a new trial of Droglican (combined chondroitin and glucosamine) for hand osteoarthritis, the PICASSO trial (NCT02823548). While we maintain that FACTUAL would have been necessary and important even in the context of the PICASSO trial, more important was that we should have recognised this earlier as a competing interest for Bioiberica.
Lessons learned: In future similar trials, (1) establish the clear expectation with industry partners that the researchers need to be notified of any relevant planned or ongoing trials at the outset and throughout the duration of the grant. (2) Task a member of the research team with periodic (6-monthly?) search of trial registers. (3) Flag any relevant trials for early discussion at TMG and with the Programme Manager as needed.

Tension in CTIMP design between the interests of NHS/funder and industry on the efficacy-effectiveness spectrum and their effect on industry engagement and independence of researchers.
A source of tension between the research team and Bioiberica in the design of the FACTUAL trial was on the role of concomitant medications. The current European Medicines Agency Guideline on Clinical Investigation of Medicinal Products Used in the Treatment of Osteoarthritis (CPMP/EWP/784/97 Rev. 1) generally advocates the exclusion of concomitant interventions, encouraging CTIMP design in osteoarthritis towards the efficacy end of the efficacy-effectiveness spectrum and was the strong preference of Bioiberica given their belief that failure to do this would result in trial data that was unacceptable to regulators. However, the NIHR HTA Programme remit is to fund research about the clinical and cost effectiveness and broader impact of healthcare treatments and tests for those who plan, provide or receive care in the NHS, i.e. towards the effectiveness end of the spectrum. It was clear in the Commissioning Brief that the control should be placebo in addition to usual care (as per NICE). Our position from the outset was that patients on stable medications for their osteoarthritis (hand or other joint) should be allowed to participate. Bioiberica expressed their concerns about this aspect of the design in writing on 20 May 2015, again in person on 21 Nov 2015.
Lessons learned: We cannot know what role this played in the failure of this trial, but it is our sense that it reduced Bioiberica's interest in the trial and their willingness to overcome other obstacles, and encouraged their initiation of a new industry-funded trial running alongside FACTUAL. It is difficult for us to see how we could have managed this differently without compromising either the usefulness of the trial for the NHS (and its fit with the commissioning brief) or our independence from industry colleagues.