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Achieving consensus on minimum data items (including core outcome domains) for a longitudinal observational cohort study in rheumatoid arthritis

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Abstract

Objectives: To obtain consensus on minimum data items for an observational cohort study in rheumatoid arthritis (RA) in the UK and to make available the process for similar studies and other rheumatic conditions.

Methods: Individuals with a diverse range of expertise and backgrounds were invited to participate in a process to propose a minimal core dataset (MCD) for research studies, commissioned by Arthritis Research UK as part of the larger INBANK project. The group included patients and representatives from clinical and academic rheumatology, outcomes science, stratified medicine, health economics, national professional and academic bodies/ committees. A process was devised based on Outcome Measures in Rheumatology Clinical Trials (OMERACT) principles to review aims/objectives, definition of scope, identification of important research questions, and selection of key domains.

Results: Following the initial multi-stakeholder meeting, subsequent teleconferences and email communications, consensus was obtained on: 1. Most important and relevant research questions; 2. Agreement on how the OMERACT Core Areas (life impact, pathophysiological manifestations, resource use and death) could form the basis of a MCD; 3. Consensus on 22 items for inclusion into a MCD. Workshops were undertaken for two essential items which required further exploration: work/social participation and co-morbidity.

Conclusions: Consensus for proposed minimal data items for long-term observational cohort studies of RA in the UK posed novel challenges and opportunities, and was largely successful. Further work is needed to select instruments for two important items and to achieve compatibility with other UK national initiatives, and more widely across Europe.

Key messages:

- Consensus was achieved for minimal data items for long-term observational cohort studies of RA
- 22 demographic & clinical items using standard measures were agreed for a proposed MCD
- Further work is needed on the appropriate instruments lacking for two important domains

INTRODUCTION

Longitudinal observational studies (LOS) provide data that many randomised controlled trials (RCTs) cannot capture, adding important insights to inform national drug commissioning and research bodies [1,2,3]. This is particularly relevant in the UK because the National Institute for Health and Clinical Excellence (NICE) adjudicates National Health Service (NHS) funded treatment strategies based largely on RCT data [4]

Modelling long-term outcomes and health economic estimations of different therapeutic approaches requires additional exploration of observational datasets [5]. Data collected in UK RA cohorts and other countries varies in clinical features and laboratory markers depending on purposes of the study [6].

Different methods of data collection for apparently similar items and terminology make comparison between cohorts and meta-analyses challenging. Greater standardisation in data capture/reporting, patient consent and disease outcomes would facilitate data pooling and analysis across datasets/biobanks, reducing chances of biased interpretation.

Increasing sample sizes by pooling studies would provide unprecedented opportunities to study less prevalent disease manifestations and subgroup analysis of important areas e.g. co-morbidity in real-life settings, opening new possibilities for comparing disease trajectories, outcomes and therapeutic impacts.

Towards this end, Arthritis Research UK (ARUK, a leading UK charity) commissioned development of a 'minimum core dataset' (MCD) for adult inflammatory arthritis (AIA), part of the larger INBANK project [7]. Linking patient information already recorded by the NHS to additional clinical information and tissue samples would promote national collaborative research into musculoskeletal conditions. Using AIA as an exemplar, a central component was development of a MCD that could be gathered prospectively from all observational datasets.

The concept of the MCD was to standardise data collection in LOS, irrespective of the primary research question in any one area of study, in order to facilitate maximal data exploitation for secondary analysis of RA outcomes by clinical and academic communities and UK regulatory authorities. Any hospital could contribute, with additional data items optional for other projects. People with an interest in development and application of standardised "core outcome sets" as described by COMET [8] were invited to participate in this process.

Although the framework of the OMERACT consensus initiative to define a core outcome set [9] was developed specifically for RCTs, the principles are applicable to LOS. To ensure wide adoption, MCDs have to be simple, self-explanatory, clinically relevant and feasible in general outpatient settings in order to engage clinicians in both district hospital and research settings, without being overly burdensome and with wider application for future national or international projects.

Although ARUK decided not to develop the infrastructure for the wider INBANK project, this first step towards a MCD for UK RA outcome studies has wider implications for LOS and was supported by the ARUK clinical studies group (CSG) [10]. We describe the process of deriving a provisional MCD for RA and its proposed content. Both might prove useful in facilitating greater research collaboration in RA and other disease areas.

METHODS

The remit was to harmonise data items that would be collected and ultimately mandated in future LOS in the UK; develop a sufficiently comprehensive dataset to address important research questions; complete the project within 12months on a limited budget.

The elected project leads (AY, AM) invited well-established and appropriate experts from many institutions to represent the wide range of disciplines likely to use INBANK to form a development team.

A process was adapted from OMERACT Filter 2.0 methodology [11], a recently-revised process of defining a core outcome set for clinical trials, and facilitated by two OMERACT representatives (MB, JK). Consensus development was centred on three main stages (Fig1).

Pre-defined break-out groups, based on appropriate mixes of patient partners, clinical and methodological expertise, with broad representation in each group, were given two specific tasks: identification of important research questions (both focused and broad) and candidate data items.

It was agreed early on that the initial scope for AIA was too wide and should be confined to RA only.

In order to maximise chances of including all relevant aspects, OMERACT Filter 2.0 explicitly separates the first step, identification of a Core Domain Set (what to measure), from the final definition of a Core Outcome Measurement Set (which includes how to measure). OMERACT advocates that at least one domain is chosen from each of four “Core Areas”: pathophysiological manifestations; life impact; death; and resource use [11]. Instruments are subsequently selected to cover each Core Domain.

Three sets of data were considered: basic identification (patient demographics), contextual factors (which could influence interpretation of outcomes) and individual outcome measures within overall core areas.

The remainder of the development process evolved as teleconferences, emails and dedicated workshops where necessary. Summaries of each focused on items lacking consensus and

appropriate measurement instruments until final agreement on all essential items was achieved.

RESULTS

The two main outcomes of this three-staged process were agreements of a key research question, and the minimum individual items for a MCD for RA which would address this and be feasible to collect in standard settings.

Identifying the most suitable research question was based on one suitable for all stages of disease and answerable within a relatively short time-period. The final question was purposefully broad and proposed to address *"What predicts clinical and health outcomes of RA patients at all stages of disease?"* with the primary analysis focusing on *"What predicts clinical and health outcomes of RA subjects with moderate disease activity (as defined using DAS28 3.2-5.1) at all stages of disease?"* This was unanimously agreed to be important, relevant to all stakeholders and scientifically robust. It was endorsed independently and subsequently ratified by the ARUK AIA CSG at its annual strategy meeting in June 2013.

It was agreed that patients with a clinician's (consultant rheumatologist) firm diagnosis of RA, irrespective of classification criteria or disease stage could be included, allowing for more homogeneous patient recruitment, examination of management issues over time, and less-well researched aspects of disease e.g. less common long-term outcomes and co-morbidities.

Emphasis was placed on items that could be collected feasibly in standard outpatient settings, and suitable and relevant for both early and established RA. Individual domains under the four key OMERACT Areas were identified as potential candidates for a MCD. Stage 1 identified 31 individual items as *potential* candidates, including demographics, important dates, contextual factors and domains from each of the four OMERACT areas. Of these, 14 items were initially proposed as essential components independently by all four discussion groups (Table 1). Agreement was not initially reached for the other 17 items, indicated as 'probable' (>50% agreement) or 'possible' (<50% agreement).

Further discussions around items core to all RA studies and for specific stages of disease resulted in the following (summarised in Table 1): 'symptom onset' removed from the essential list because of doubtful accuracy and importance in established RA; 7 items in the 'probable' category (weight, height, pain, fatigue, function, QoL/utility, co-morbidity) and two items in the non-essential category (smoking, family history) were finally agreed as essential items; consensus on 22 individual items for inclusion, three of which were imbedded in the EQ5D.

Decisions on the majority of measurement instruments were straight-forward, based on well-established validated tools. Absence of disease-specific validated tools was recognised for: participation/work; fatigue; and co-morbidity. Parallel small group teleconferences and/or dedicated workshops of team members played a key role on further decisions around these items. Following an ARUK workshop on Fatigue, it was decided that a simple numerical rating scale (NRS) as opposed to a multi-dimensional instrument would be more appropriate for a minimal dataset. The 11-point NRS of the Bristol RA Fatigue Multi-Dimensional Questionnaire (BRAF MDQ) was agreed as most appropriate [12].

Participants agreed that it would be reasonable to obtain consent for linkage for cause and date of death. In recognition of future opportunities for evaluating drug history and co-morbidities as informatics systems become better integrated in the UK, linkage could also include two 'possible items', hospital episodes and joint surgery, available from National Databases and Primary and Secondary Care Information Systems.

Items identified as important for many research questions, but not essential for all, could be included in optional 'add-on' studies (Table 1). ACR/EULAR classification criteria were excluded as they are not formally used by most clinicians in routine clinical practice and difficult to apply from notes review in established disease.

The group distilled their combined opinions on the relative value and feasibility of collection based on clinical experience and discussion. All the provisional items considered have an

evidence base as measures of, and predictors for, outcomes in RA. The development team included BSR representatives examining standard coding terms for rheumatic diseases to advise on precise definitions, clinical terms, validation rules and data entry consistency (e.g. dates). Figure 1 is a diagrammatic summary of the process. Table 1 shows agreed items for a MCD for RA, with corresponding instruments for data collection.

Discussion

Through the consensus process devised by OMERACT, the important initial step of agreeing a research question of universal interest was achieved by stakeholders, who also met the challenge to balance unfeasibly numerous measures against the need for the smallest possible dataset that could still answer a wide range of research questions robustly. The final research question agreed concerned outcomes of patients with moderate disease activity (and ineligible for biologics in the UK). It is notable that the AIA CSG independently identified the relative paucity of outcome data in moderate RA at the same time, and set this as a research priority for 2014/5.

The group took into account patients' perspectives and the needs of clinical engagement with both district hospital and research-centre settings. The conceptual model underlying OMERACT Filter 2.0 methodology [11] was a crucial part of this multi-step process, resulting in successful step-wise selection of key domains under four Core Areas (life impact, death, pathophysiological manifestations and resource use), which firstly guided selection of core domains, and subsequently selection of appropriate candidate instruments. This strategy minimised the risk of missing out important domains.

Twenty-two items were proposed as essential for a MCD (Table 1), consensus achieved through an opinion-based process. The absence of a formal multi-stage Delphi process because of time constraints could be considered a weakness. We believe these weaknesses were offset by achievement of the main aims of this initiative: the multi-disciplinary approach with wide ranges of expertise and backgrounds; compliance with concepts based on well-

established OMERACT methodology which includes step-wise approaches towards item selection based on existing evidence and expert opinion; strategic planning so that the process was completed within time and cost targets initially set out.

Many of the MCD items are available within the NHS records system, but the domain measurements require clinical input. For two domains, participation/work and comorbidity, instruments for data-collection still need to be finalised. There was unanimous agreement that both should be embedded in routine data collection.

The MCD-development process described here could prove beneficial towards standardising data collection, allowing comparisons and data pooling between cohorts and countries. Standardising outcomes has been proposed as a solution to the problems of inappropriate and non-uniform outcome selection in clinical trials [13]. OMERACT advocates use of core outcome sets in clinical trials designed using consensus techniques [14] which formed the basis of the current process for a provisional MCD, albeit focussed on LOS in RA.

Our provisional dataset requires validation in routine clinical settings. Work is currently in progress both nationally & internationally on easily administered and validated measures for participation/work and co-morbidity. Close liaison with BSR will avoid duplicate work streams and maximise levels of consistency between datasets on clinical terms and data entry for all items.

In conclusion, the development of a provisional list of minimum data items (including core outcome domains and their instruments) for LOS and research databases in RA has posed novel challenges and opportunities. The process followed was largely successful, achieved in less than 12months, and could help development of larger-scale projects and in other disease areas. Well-coordinated data capture with national linkage where possible could be an important way forward, optimising data for research which would have an ultimate impact on patient care.

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