Global mapping of randomised trials related articles published in high-impact factor medical journals: a cross-sectional analysis

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Abstract

Background Randomised controlled trials (RCTs) provide the most reliable information to inform clinical practice and patient care. We aimed to map the global clinical research publication activity through RCTs related articles in high-impact factor medical journals over the past five decades.

Methods Cross-sectional analysis of articles published in the highest ranked medical journals with an impact factor > 10 (according to Journal Citation Reports published in 2017). We searched PubMed/MEDLINE (from inception to December 31, 2017) for all RCTs related articles (e.g. primary RCTs, secondary analyses and methodology papers) published in high-impact factor medical journals. For each included article, raw metadata were abstracted from the Web of Science. A process of standardization was conducted to unify different terms and grammatical variants and to remove typographical, transcription, and/or indexing errors. Descriptive analyses were conducted (including the number of articles, citations, most prolific authors, countries, journals, funding sources and keywords). Network analyses of collaborations between countries and co-words were presented.

Results We included 39305 articles (period 1965-2017) published in forty journals. The Lancet (n=3593; 9.1%), the Journal of Clinical Oncology (n=3343; 8.5%), and The New England Journal of Medicine (n=3275 articles; 8.3%) published the largest number of RCTs. 154 countries were involved in the production of articles. The global productivity ranking was led by the United States (n=18393 articles), followed by the United Kingdom (n=8028 articles), Canada (n=4548 articles) and Germany (n=4415 articles). Seventeen authors who published 100 or more articles were identified; the most prolific authors were affiliated with Duke University (United States), Harvard University (United States), and McMaster University (Canada). Main funding institutions were the National Institutes of
Health (United States), Hoffmann-La Roche (Switzerland), Pfizer (United States), Merck Sharp & Dohme (United States) and Novartis (Switzerland). The 100 most cited RCTs were published in 9 journals, led by The New England Journal of Medicine (n=78 articles), The Lancet (n=9 articles) and JAMA (n=7 articles). These landmark contributions focused on novel methodological approaches (e.g. “Bland-Altman method”) and trials on the management of chronic conditions (e.g. diabetes control, hormone replacement therapy in postmenopausal women, multiple therapies for diverse cancers, cardiovascular therapies such as lipid-lowering statins, antihypertensive medications, antiplatelet and antithrombotic therapy).

Conclusions Our analysis identified authors, countries, funding institutions, landmark contributions and high-impact factor medical journals publishing RCTs. Over the last 50 years, publication production in leading medical journals has increased with research leadership of Western countries, but with very limited representation from low and middle-income countries.

Background

Randomised controlled trials (RCTs) are considered one of the simplest and most powerful tools for assessing the safety and effectiveness of treatment interventions [1-3]. When appropriately designed, conducted and reported, RCTs can produce an immediate impact on clinical practice and patient care [4].

The evolution of RCTs has been an enduring and continuing process [5-15]. Since the 1970s, the publication landscape for RCTs has exhibited an exponential growth. For example, a 1965-2001 bibliometric analysis of the literature identified 369 articles published in 1970 compared to 11159 published in 2000 [5]. The development of clinical trial registries (such as clinicaltrials.gov) [9,10], the exponential increase in journals
publishing trial protocols, results and secondary studies, and growing support for data-sharing policies [11,12] have created an open research environment of transparency and accountability. Furthermore, the publication of reporting guidelines (such as CONSORT and SPIRIT) [4,13-15] have served to facilitate the transition between research and reporting to ensure standardisation and ease of readability.

RCTs published in major medical journals are highly cited and have an instrumental role in clinical practice [5,16,17]. Previous studies have focused on the quality of reporting of methods and results of RCTs [18-22], and publication practices [23-28] in selected samples of articles published in high impact factor (IF) medical journals. However, to the best of our knowledge, there have been no mapping studies of major medical journals investigating the most common subjects, most productive scientists and countries, most prolific journals and “citation classics” across multiple specialties.

The objective of this study was to describe and characterise the global clinical research publication activity through RCTs articles published in high IF medical journals during the past decades.

Methods

Eligibility criteria

This cross-sectional analysis investigated RCTs related articles (that is, primary RCTs, secondary analyses and methodology papers using clinical data) published in major medical journals. We excluded narrative reviews, systematic reviews, meta-analyses, pool-analyses, letters and newspaper articles. All RCT related articles indexed in PubMed/MEDLINE had to be published in one of the major medical journals with an IF exceeding 10 (2016 IF according to the Journal Citation Reports [JCR] published in June
These medical journals were chosen as they were determined to publish clinical research with scientific merit and clinical relevance (see BOX for a list of included medical journals).

**Search**

On March 22, 2018 we systematically searched MEDLINE through PubMed (National Library of Medicine, Bethesda, MD, United States) for all RCTs related articles published in high IF medical journals (from inception to December 31, 2017). A senior information specialist (AA-A) and a clinical epidemiologist (FC-L) designed an electronic literature search using a validated research methodology filter for RCTs (with 97% specificity and 93% sensitivity) [29]. The search was peer reviewed by members of the study team, including a second (senior) information specialist (RA-B). The full search strategy is provided in Additional file 1. On May 7, 2018 we searched the Web of Science (WoS) (Clarivate Analytics, Philadelphia, PA, United States) by using PubMed IDs (PMIDs) from the PubMed/MEDLINE searches. Merging MEDLINE with other citation indices such as the WoS combines the advantages of MEDLINE (e.g. Medical Subject Headings [MeSH], a comprehensive controlled vocabulary for indexing journal articles) with the relational capabilities and data of the WoS [30].

**Data extraction and normalisation**

For each included article, raw (meta)data on the journal and article titles, subject category, the year of publication, keywords, and the authors’ names, institutional affiliation(s), funding source, and country was downloaded online through the WoS by one researcher (A-AA). We also used the WoS to determine the extent to which each article had been cited in the scientific peer-review literature using the “times cited” number (that
is, the number of times a publication has been cited by other publications). Two researchers (FC-L, RA-B) verified independently the data to minimise potential information errors. A process of normalisation was conducted by two researchers to bring together the different names of an author or country, and keywords (further details are available in Additional file 2). Specifically, one researcher (AA-A) checked the names by which an individual author appeared in two or more different forms (for example, “John McMurray” or “John J. McMurray” or “John J.V. McMurray”) using coincidence in that author’s place(s) of work as the basic criterion for normalisation (for example, University of Glasgow, Scotland, United Kingdom) [31], and a second researcher (FC-L or RA-B) verified data. A threshold of 30 articles was applied to review 200 names by which an individual author appeared in two or more different forms.

We extracted both “author keywords” and “keyword plus,” which are automatically assigned by the WoS from the titles of the references of the articles, as topical (also called textural, linguistic, or semantic) data [32]. To ensure consistency in the data, one researcher (RA-B) corrected keywords unifying grammatical variants and using only one keyword developed names of the same concept (for example, “randomized trial” or “randomized clinical trial” or “randomized controlled trial” or “randomised controlled trial”). In addition, the same researcher (RA-B) removed typographical, transcription and/or indexing errors, and a second researcher (FC-L) verified data. All potential discrepancies were resolved via consensus amongst these investigators. All these data were collected and entered into a Microsoft Access® (Microsoft, Seattle, WA, United States) database between May 7, 2018 and January 9, 2019.

Data analysis

We analysed data including the number of articles, citations, signatures (or total number
of authors included in all the articles of each author), collaboration index (that is the mean number of author’s signatures per article), countries, journals and keywords. Data were summarised as frequencies and percentages for categorical items. The most prolific authors (> 100 articles), countries (> 100 articles), funding institutions (> 100 articles), and the most cited papers (“top-100 citation classics”) were identified. Network plots were generated for intense scientific collaboration between countries (applying a threshold of 100 articles in collaboration).

We conducted exploratory analyses of topical data using a set of unique keywords or and their frequencies to examine the topic coverage, major topics (“word clouds” of keywords) and their interrelations (“co-words networks”) in RCT articles. The main goal in topical analyses are to understand the topical distribution of a dataset - what topics are covered and how much of each topic is covered in a scientific discipline [32]. The most frequently used keywords were identified for most prolific journals (with at least 1000 articles).

Based on most frequently used keywords (with at least 500 articles), a word cloud was created from text that the user provides and places more emphasis on words that appear with greater frequency in the source text. A “co-words network” was created to illustrate the co-occurrence of highly frequent words in the articles (applying a threshold of 100 articles in collaboration). The network analysis was carried with the use of PAJEK (University of Ljubljana, Slovenia) [33], a software package for large network analysis that is free for non-commercial use, to construct network graphs. PRISMA checklist [34] (http://www.prisma-statement.org/) guided the reporting of the present analysis (and is available in Additional file 3).

Results

There were 39329 records identified by the PubMed/MEDLINE search (Fig 1). A total of 39305 articles met the study inclusion criteria (Additional file 4), after 24 records were
excluded (Additional file 5). Table 1 details the general characteristics of the articles.

Publication trend
The number of articles increased exponentially over the 1965-2017 period (Fig 2).
Approximately 60% (n=23635) of the articles have been published since 2000.

Journals and subject category
Forty journals published 39305 articles and 23.8% of them (n=9355) were published by four journals with an IF > 30. The Lancet (9.1%; n=3593), the Journal of Clinical Oncology (8.5%; n = 3343), and The New England Journal of Medicine (8.3%; n=3275) published the largest number of articles, followed by The BMJ (6.4%; n=2516) and Circulation (5.9%; n=2331). Most articles were classified in “medicine, general & internal” (30.7%; n=13688), “cardiac & cardiovascular systems” (13.1%; n=5828), or “oncology” (12.9%; n=5760) according to the WoS journal categorisations (Table 1).

Authors, institutions and countries
Most articles (62.3%; n=24496) were written by 7 or more authors and only 11.4% (n=4469) of articles were written by 3 or less authors. The first authors of the articles were based most commonly in North America and Western Europe; first authors from the United States were responsible for 36.9% (n=14508) of the articles (Table 1). We identified 17 authors who published 100 or more articles (Table 2). All the most productive authors were male. The most prolific authors were Robert M Califf with 239 articles (from Duke University, United States), Eugene Braunwald with 218 (from Harvard University, United States), Salim Yusuf with 217 (from McMaster University, Canada), Eric J Topol with 212 (from Scripps Translational Science Institute, United States), Harvey D White with 186
Overall, 154 countries worldwide contributed to the analysed articles. The publication productivity ranking for countries (Table 3) was led by the United States (n=18393 articles with 3.4 million citations), followed by the United Kingdom (n=8028 articles with 1.3 million citations), Canada (n=4548 articles with 1.0 million citations) and Germany (n=4415 articles with 0.9 million citations). There were 37 countries with at least 100 articles in co-authorship. Fig 3 shows a visual representation of the most intense collaborative network between these 37 countries, in which we can see the relationships of some countries with respect to others and the position that each occupies in the network.

**Funding source**

16485 articles (41.9%) reported sources of funding. The 40 most frequent funding institutions (with 100 or more articles) are listed in Table 4. The main funders were the National Institutes of Health (NIH) with 7422 articles, Hoffmann-La Roche (n=1188), Pfizer (n=1139), Merck Sharp & Dohme (n=1097) and Novartis (n=1052).

**Most cited articles**

Overall, included articles received 5.9 million citations, of which 83.1% citations (n=4950604) corresponded to 15142 (38.5%) articles with more than 100 citations. There were 641 (1.63%) articles with more than 1000 citations that accumulated 20.7% of the total citations (n=1234462). The most cited articles by number of citations (“100 citation classics”) are listed in Table 5. All of the most cited papers were published in English. These most cited articles were published in 9 journals, led by *The New England Journal of*...
*Medicine* with 78 articles, followed by *The Lancet* (n=9) and *JAMA* (n=7). The list of most cited papers contained innovative research methodologies. For example, the most cited article was a method paper published in *The Lancet* (“Bland-Altman method”) [35]. This seminal paper changed how method comparison studies are performed in clinical research. The list of the most cited papers also reflected important studies examining the health effects of pharmacological interventions on patients with chronic diseases. Common themes in major advances in health interventions included diabetes control [36-41]; the effects of hormone replacement therapy in postmenopausal women [42,43]; therapies for diverse cancers such as glioblastoma, colorectal cancer, breast cancer, melanoma and hepatocellular carcinoma [44-50]; important interventional studies in the field of clinical cardiology such as lipid-lowering statin therapy trials, antihypertensive trials, and antiplatelet and/or antithrombotic trials [51-63].

**Common keywords**

The most commonly used article keywords were “clinical trial” (16.1%; n=6332 papers), followed by “therapy” (10.8%; n=4267), “randomised controlled trial” (6.6%; n=2587), “chemotherapy” (5.6%; n=2224), “risk” (5.1%; n=2026), “efficacy” (4.9%; n=1933), and “double-blind” (4.9%; n=1929). The most frequently used keywords in the most prolific journals are shown in Table 6. In addition, exploratory analyses of word clouds and networks based on keywords (co-words) showed a broad range of topics covered (see Additional file 6).

**Discussion**

In this cross-sectional analysis, we presented a global mapping of RCTs related articles published in high IF medical journals for the period 1965–2017. We identified the most prolific scientists, institutions and countries, most common subjects and topics, “citation
classics” and most prolific high IF medical journals from multiple specialties over the last 50 years.

In general, we found a strong clustering of articles published in British and American medical journals (The Lancet, Journal of Clinical Oncology, The New England Journal of Medicine, The BMJ, Circulation, JAMA, JACC, and Diabetes Care accounted for 53% of RCTs related articles). Many of these journals have been developed by active medical associations, both nationally and internationally. We hypothesize that different publishing patterns between journals may potentially reflect editorial policies and/or preferences, with some general medicine journals (such as The Lancet and The New England Journal of Medicine) and specialty journals (such as Journal of Clinical Oncology and Circulation), being more interested in and/or promoting the publication of RCTs. In contrast, a substantial amount of these articles are behind publication paywalls (very few of the medical journals in our study sample are Open Access) and thus, research results may not be accessible to a large fraction of the scientific community and society as a whole, including clinicians (and patients) who may want them to help inform their clinical practice.

The results of this study highlight the expanding collaborative networks between countries in multiple regions, revealing a discernable scientific community, with the most productive countries having an important number of collaborations. Publication activity efforts were global during the study period, with articles from scientists and institutions in more than 150 different countries. However, the scientific community is centered on a nucleus of scientists from Western countries – the most intense global collaborations took place between the United States, United Kingdom and Canada. The presence and influence these
countries have on biomedical research [64-66] may be due to their large multi-stakeholder research partnerships, greater financial investment in clinical research, and high population of active scientists and research centers compared to other countries.

Publication activity worldwide shows that low and middle-income countries have low levels of articles in high IF medical journals. Difficulties in healthcare, education and research systems, information access and communication, language barriers, economic and institutional instability, all represent challenges (and clear disadvantages) for productivity in low and middle-income regions. In addition, restrictions and difficulties in conducting clinical research in resource-poor situations result in the exclusion of many of these countries from planning, conduct and publication of RCTs [67-69]. As might be expected, our results support previous findings that low and middle-income countries [31,70,71] had minimal contributions in articles published in major medical journals. For example, a previous study [70] showed that most of the authors of original papers published in five high impact general medical journals (including The New England Journal of Medicine, The Lancet, JAMA, The BMJ and Annals of Internal Medicine) were more frequently affiliated with institutions in the same country as the journal. To address some of these problems, scientists, institutions and funders should promote collaborations (beyond historical, cultural and political factors) to share knowledge, expertise and innovative methodologies for clinical research. This may involve partnerships with Western countries to support capacity and resource development and research training.

RCTs related articles were published most often in high IF medical journals devoted to general and internal medicine, cardiology and oncology (nearly 57% of all articles). Similarly, the lists of the most cited articles identified topics which reflect major advances in the management of chronic conditions (such diabetes, cardiovascular disorders and
The large relative productivity in general internal medicine, cardiology and oncology may be explained by the important role of randomised evidence to novel treatments and preventive strategies for these chronic diseases. In line with previous research [72-75], most of these highly-cited RCTs addressed interventions for burdensome conditions that are health priorities in Western countries [76,77]. Funding of (international, collaborative) RCTs may come from varying sources including commercial and non-commercial sponsors. However, previous analyses of RCTs related articles published in high IF journals have suggested study sponsors may influence how RCTs are designed, conducted and reported, sometimes serving financial rather public interests [78]. Given that research funding is often restricted, it is the responsibility of scientific community to use the resources available most efficiently when exploring research priorities to afford research users and population health needs [76,77,79,80].

Our findings suggest that women are vastly underrepresented in the group of most prolific scientists publishing in high-impact medical journals. This is in direct contrast to recent studies that have identified a gender gap in research publications [81-84]. For example, a previous study [84] showed that women in first authorship positions increased from 27% in 1994 to 37% in 2014 in leading medical journals (including *Annals of Internal Medicine*, *JAMA Internal Medicine*, *The BMJ*, *JAMA*, *The Lancet*, and *The New England Journal of Medicine*), but progress has plateaued or declined since 2009. There is an urgent need to investigate the underlying causes of the potential gender gap in order to help to identify publication practices and strategies to increase women's influence [82,84].

There are several limitations to our study. First, we characterised knowledge structures generated by articles published in major medical journals included in the WoS database. Although the publication production analysed has been drawn from an exhaustive analysis of the biomedical literature, it is possible that the search missed some relevant articles
(and journals). Some reports may be published in journals without being indexed as RCTs, making them difficult to identify. Second, as in many bibliometric analyses, the importance of normalising the different names of an author, country, and funding sources is fundamental to avoiding potential errors. We conducted a careful manual validation of the references and textual data to avoid typographical, transcription and/or indexing errors. However, we recognize this procedure does not assure complete certainty. Third, the affiliation addresses of authors do not necessarily reflect the country where the research was conducted, nor the research funding source. Fourth, topical analysis extracting a set of unique keywords, word profiles and co-words may indicate intellectual organization in publication production, albeit with inherent limitations [85,86]. Fifth, use of citation analysis carries with some problems [87-91]. There is a potential length time-effect bias which puts more recent articles at a disadvantage. In addition, the biomedical literature is rich in barriers and motivations for publication and citation preferences [87], including self-citation (bias towards one’s own work) [88], language bias (bias towards publishing and citing English articles), omission bias (bias purposely not citing competitors), and selective reporting and publication bias (bias withholding “negative” results from publication and citation) [89-92]. In addition, citations are also treated as equal regardless of whether a research is being cited for its positive contribution to the field, but also for being criticized. Finally, our methods represent only a mapping approach which could be complemented further by more detailed analyses, for example examining the content, the reporting and reproducible research practices through research of research (“meta-research”) studies [92-95].

Conclusion

The global analysis presented in this study provides evidence of the scientific growth of RCTs related articles published in high IF medical journals. Over the last 50 years,
publication activity in leading medical journals has increased with leadership of Western
countries (most notably, the United States), but with very limited representation from low
and middle-income countries. Our analysis contributes to a better conceptualization and
understanding of RCTs articles and identified the main areas of research, the most
influential publication sources chosen for their scientific dissemination and the major
scientific leaders. Given the dynamic nature of the field, it will be interesting to see
whether the growth trend remains in the coming years, and how the characteristics of the
field change over time.

Declarations

Ethics approval and consent to participate
This study outlines a cross-sectional analysis of secondary data and hence does not
require ethical approval or consent to participate.

Consent to publish
Not applicable.

Availability of data and materials
With the publication of this manuscript, the full dataset will be freely available online in
the Open Science Framework (https://osf.io/r2vw5/), a secure online repository for
research data.

Competing interests
The authors declare that they have no competing interests to declare.

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Author's contributions
FC-L, RA-B, RT-S and AA-A contributed to conceptualizing and designing the study. FC-L and AA-A supervised the study. AA-A curated data. AA-A and FC-L performed data analysis and visualizations. FC-L, RA-B, LC, BH, RT-S, DM, and AA-A interpreted the study findings. FC-L drafted the first version of the manuscript. RA-B, LC, BH, RT-S, DM, and AA-A commented for important intellectual content and made major revisions. All authors read and approved the final version of the manuscript. All authors meet the ICMJE criteria for authorship. FC-L and AA-A accept full responsibility for the finished manuscript and controlled the decision to publish.

Declaration of transparency
FC-L affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Additional Files

Additional file 1: Full strategy in PubMed/MEDLINE (.docx)

Additional file 2: Data extraction and normalisation processes (.docx)

Additional file 3: Reporting checklist (.docx)

Additional file 4: List of PMID for included articles (.docx)

Additional file 5: List of excluded articles (.docx)

Additional file 6. Exploratory analysis of topical data (.docx)

Figures
**Figure 1.** Flow diagram with selection of articles.

Records retrieved through PubMed/MEDLINE search (n=39329)

Excluded (n=2):
- No record in Web of Science (n=2)

Records retrieved through Web of Science (n=39327)

Relevant publications with PubMed ID – PMID (n=38040)

Excluded (n=22):
- Indexing errors (n=5)
- Duplicate (n=8)
- Corrections and/or errata (n=9)

Complementary manual search by title (n=1287)

Articles included in analysis (n=39305)
Figure 2. Number of articles by year of publication.

Figure 2

Number of articles by year of publication.
Global collaborative network between countries.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

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