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Complete List of Authors:	Fitzpatrick, Tiffany; Ontario SPOR Support Unit, Perrier, Laure; St. Michael's Hospital, Li Ka Shing Knowledge Institute Tricco, Andrea; Li Ka Shing Knowledge Institute of St Michael's Hospital; University of Toronto, Dalla Lana School of Public Health Straus, Sharon; St. Michael's Hospital, Li Ka Shing Knowledge Institute Jüni, Peter; St. Michael's Hospital, Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute; University of Toronto, Department of Medicine Zwarenstein, Merrick; Institute for Clinical Evaluative Sciences; Western University Schulich School of Medicine and Dentistry, Department of Family Medicine Lix, Lisa; University of Manitoba, Manitoba Centre for Health Policy Smith, Mark; University of Manitoba, Community Health Sciences Rosella, Laura; University of Toronto, Dalla Lana School of Public Health; Institute for Clinical Evaluative Sciences Henry, David; University of Toronto, Dalla Lana School of Public Health; Institute for Clinical Evaluative Sciences
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Authors:

***Tiffany Fitzpatrick**, MPH [a]	TiffanyFitzpatrick@ossu.ca
Laure Perrier, PhD MLIS MEd [b]	L.Perrier@utoronto.ca
Andrea C. Tricco, PhD MSc [c d]	TriccoA@smh.ca
Sharon E. Straus, PhD MD MSc FRCP(C) [c]	Sharon.Straus@utoronto.ca
Peter Jüni, MD FESC [e f g]	Peter.Juni@utoronto.ca
Merrick Zwarenstein, MBBCh MSc PhD [h i]	Merrick.Zwarenstein@schulich.uwo.ca
Lisa M. Lix, PhD P.Stat MSc [j k]	Lisa.Lix@umanitoba.ca
Mark Smith, MSc [k]	Mark_Smith@cpe.umanitoba.ca
Laura C. Rosella, PhD MHSc [d i l]	Laura.Rosella@utoronto.ca
David A. Henry, MB ChB MRCP FRCP [d g i]	David.Henry@utoronto.ca

Affiliations

a Ontario Strategy for Patient-Oriented Research (SPOR) SUPPORT Unit, Toronto, ON, Canada;
b Gerstein Science Information Centre, University of Toronto Libraries, Toronto, ON, Canada;
c Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada;
d Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada;
e Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada
f Department of Medicine, University of Toronto, Toronto, ON, Canada;
g Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
h Department of Family Medicine, Schulich School of Medicine, University of Western Ontario, London, ON, Canada;
i Institute for Clinical Evaluative Sciences, ON, Canada
j Department of Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada
k Manitoba Centre for Health Policy, University of Manitoba, Winnipeg, MB, Canada
l Public Health Ontario, Toronto, ON, Canada

***Corresponding author contact details:**
Mailing Address: 6th Floor, 155 College St., Toronto, ON, Canada, M5T 3M6
Telephone: 416-978-8364

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ABSTRACT

Introduction: Well-conducted randomized controlled trials (RCTs) provide the least biased estimates of intervention effects. However, RCTs are costly and time-consuming to perform and long-term follow-up of subjects may be hampered by lost contacts and financial constraints. Advances in computing and population-based registries have created new possibilities for increasing the value of RCTs by post-trial extension using linkage to routinely collected administrative/registry data in order to determine long-term interventional effects. There have been recent important examples, including 20+ years follow-up studies of trials of pravastatin and mammography. Despite the potential value of post-trial extension, there has been no systematic study of this literature. This scoping review aims to characterize published post-trial extension studies, assess their value, and identify any potential challenges associated with this approach.

Methods and analysis: This review will use the recommended methods for scoping reviews. We will search MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The draft search strategy is included in this protocol. Review of titles and abstracts, full texts of potentially eligible studies, and data/information extraction will be conducted independently by pairs of authors. Eligible studies will be RCTs that investigated healthcare interventions that were extended by individual linkage to administrative/registry/electronic medical records data after the completion of the planned follow-up period. Information concerning the original trial, characteristics of the extension study, any clinical, policy or ethical implications and methodological or practical challenges will be collected using standardized forms.

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Strengths and limitations of this study

- Provides the first review of post-trial extension studies, specifically those using secondary data sources, to identify long-term participant outcomes.
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- The heterogeneity of content areas covered by this methodology may provide challenges in synthesizing the results into succinct conclusions or recommendations.

INTRODUCTION

Randomized controlled trials (RCTs) are widely considered the gold standard for generating clinical evidence. High quality RCTs require considerable human and financial resources and, in some cases may require commitments spanning many years. Despite these investments, follow-up of patients typically ceases after the trial is completed as planned and the results have been released to inform clinical practice or regulatory decisions. At this point it can be said that a trial becomes 'dormant', as the data are no longer used for new research.

However, dormant trials offer considerable potential for new research, including reanalysis to confirm primary trial outcomes, analysis of new clinical outcomes and follow-up of participants to

assess the potential long-term benefits and harms of interventions [1]. According to a scoping review by Ebrahim et al., re-analysis appears to be a fairly uncommon event [2]. Their review identified only 37 examples of trial re-analyses [2]. However, they did not look at additional uses of study data, such as post-trial extensions to assess long-term outcomes. Given growing demand for transparency in research, open data and data sharing, and tight fiscal budgets for research, the re-analysis, validation and re-activation of dormant trials is an attractive strategy to maximize the value gained from large investments in RCTs.

Arguably, the Diabetes Control and Complication Trial (DCCT) study group is a trailbreaker in the re-use of trial data and post-trial follow-up [3]. Since the completion of their original trial in the early 1990s, the group has been involved in over 200 analyses using data from the original DCCT or its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) [4]. Likewise, in recent years there have been several high-profile examples of trial extension studies, where authors follow participants for decades after trial closure using linkage to secondary data sources to assess potential long-term effects. For example, the 25-year follow-up of the Canadian National Breast Cancer Screening Study (CNBCSS) was published in 2014. Long-term follow-up was achieved by linkage to population-based cancer registry and vital statistics data [5]. This study found that annual mammography in women aged 40-59 did not reduce mortality from breast cancer when compared to usual care [5]. Another notable example is the 20-year follow-up of the West of Scotland Coronary Prevention study (WOSCOPS), which showed a lifetime benefit of improved survival and reduced cardiovascular disease following only five years of statin therapy [6].

These are only two prominent recent examples of trials that have been extended beyond the original planned term using secondary linked data sources; both of which provided important clinical findings. It is not clear, however, how many trials have been extended in this way. On the surface, this appears to be a fairly uncommon practice; particularly in relation to the number of high-impact RCTs that are completed each year. While some trials plan to study outcomes using secondary data sources as part of the original protocol, and some are designed as 'registry trials', few seem to have been extended as an independent exercise after the original study was completed.

There are several reasons why an investigator would be interested in conducting a post-trial extension study. Most obvious would be the desire to estimate the potential long-term benefits or adverse effects of an invention [7]. Specifically, it is possible to map the accrual or loss of benefits over time with greater certainty. For instance, the extension of the WOSCOPS revealed a 'legacy' effect of a relatively short period of statin treatment, still visible after 20 years.[6] Post-trial extensions could also provide longer observations regarding the natural history of a disease among a well-characterized control group, the persistence of adherence to therapy, and the patterns and effects of co-interventions introduced after trials end.

While highlighting the potential benefits of post-trial extension we acknowledge that it is uncertain whether the efforts and potential challenges will always be worthwhile, particularly in terms of novel findings that have important clinical or policy relevance. But the feasibility and low cost makes these exercises attractive. Advances in the availability of linkable population data sets and analytical capacity make this option more feasible than in the past, so we believe it will become an increasingly common activity. The relatively low cost of post-trial linkage studies is illustrated by WOSCOPS. The original trial cost approximately £20 million to complete, whereas the follow-up study was conducted for only £15,000 [8].

It will be important for researchers to consider potential methodological, logistical and ethical challenges associated with post-trial extension studies. For instance, post-trial extensions are essentially observational, with management decisions influenced by practice guidelines rather than trial protocols. This introduces a potential for unmeasured time-varying confounding with threats to internal validity. This will be especially important in the case of interventions that are found to be effective and are rapidly adopted by control group members after trial termination. This could

attenuate any long-term effects identified by the follow-up study, especially if cross-overs cannot be identified in the available secondary data sources and cannot be accounted for the analysis. Logistical challenges will include unavailability of data, storage in paper records and lack of linkable fields in the research data, for instance when records have been de-identified, but the linkage key is no longer available. Finally, it is unclear how research ethics boards will respond to requests to approve linkage of individual patient data when this was not specified in the original clinical trial consent form.

In the light of these considerations the principal objective of this scoping review is to quantify and characterize published post-trial extension studies, assess their value, and identify potential research gaps, logistical and ethical challenges associated with this approach. Upon completion of this review, we hope to report on several issues:

1. The number of post-trial extension studies that have been completed using health administrative or registry data;
2. The types of outcomes assessed in these studies and how well they were detected (i.e., the type(s) of data and if there was any validation process);
3. The main challenges associated with conducting post-trial extensions (e.g., achieving data linkage, obtaining ethics approval, obtaining agreement from the original investigators, analytical challenges);
4. The extent to which the original trial findings were altered with extended follow-up;
5. The costs and time involved in performing post-trial extensions; and
6. The likely clinical and policy implications of new information generated through post-trial extensions.

METHODS

We will undertake a scoping review to examine the literature covering post-trial extensions of RCTs using linked secondary data sources, such as health administrative or population registry data and electronic medical records, to ascertain long-term clinical outcomes of participants. The scoping review methodology was selected to map the literature in this emerging area. [6,9-10]. Importantly, a scoping review will enable a broad examination of the nature, extent, and range of the research activity and help identify gaps in the current literature. Specifically, we will follow the standard methodological guidelines for conducting scoping studies, specifically those set out by the Joanna Briggs Institute handbook, and will report according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9-11].

Our protocol draws upon the framework outlined by Arksey and O'Malley [10], which outlines the following five stage approach to conducting a scoping review: 1) developing the research question; 2) identifying all relevant studies; 3) selection of studies; 4) data extraction; 5) summary and reporting of results; and 6) consultation.

Study selection

Search strategy

The draft search strategy (for MEDLINE) was developed by an information specialist (LP), who was instrumental in maximizing its sensitivity and specificity and ensuring its feasibility. It will be assessed by a second information scientist according to the Peer Review of Electronic Search Strategies (PRESS) checklist [12] and will be refined as dictated by early results. The search strategy includes MeSH and text words related to randomized controlled trials, post-trial and long-term follow-up studies, and data linkage (including specific database types). Notably, since this is an emerging area of interest with little specialization, there are currently no dedicated indexing terms

for this study type. Further, there is little standardization in how this study type is described. As such, the search strategy relies on a variety of non-standard search terms; e.g. “X-year follow-up”.

The search strategy will be replicated in the EMBASE and the Cochrane Central Register of Controlled Trials databases. The search will be limited to English language articles; no other restrictions will be placed on the search strategy.

We will search for additional articles by utilizing the Related Articles feature in PubMed for articles included in the scoping review and those deemed highly relevant by the core research team. This strategy was selected because previous work has shown that the Related Articles feature in PubMed can identify relevant studies with a relatively low screening burden of new records per review [13]. We decided to do this additional search as our initial scan identified several relevant studies that did not explicitly refer to data linkage in their abstract and would subsequently be missed by our search strategy. Finally, we will leverage the personal libraries and content knowledge of our clinical and epidemiological expert authors to identity any additional studies for inclusion.

Our MEDLINE search strategy can be found in **Appendix A**. Upon completion, the searches from each of the above databases will be documented and references imported into a reference management software program, where duplicates will be removed. All references will be stored and shared using a reference management software program (e.g. Reference Manager, Version 12).

Study selection

Prior to screening, we will conduct a calibration exercise with a sample of 50 retrieved citations to assess the reliability of our level 1 screening of title and abstracts. We will aim for agreement of at least 95% before beginning title and abstract screening. Subsequently, the abstracts and titles of all retrieved references will be independently reviewed by two authors to identify potentially eligible studies for inclusion. Disagreements will be put forth for full-text review. The full text of all eligible citations will also be examined in detail by two independent reviewers. In cases of disagreement, consensus will be reached through discussion or be resolved by a third reviewer.

Studies will be eligible for inclusion if they satisfy all of the following criteria:

1) *Population:* any definable (human) patient population, including both children and adult populations. All countries and sub-populations will be included;

2) *Intervention*: any health-related intervention applied at the individual level, such as pharmaceutical interventions, lifestyle modification, screening practices, etc.;

3) *Outcomes* (primary or secondary): any health-related event, such as onset of disease, specific complications, health system outcome, or death that are considered likely to be detectable in administrative/registry data;

4) *Design*: limited to clinical trial that involve either individual or cluster randomization of individuals to an intervention or control group. We will include randomized crossover designs, adaptive designs, and factorial designs. We will not include quasi-experimental designs, self-controlled studies or those using interrupted time series analysis outside of a randomized controlled trial;

5) *Extension methods*: follow-up of trial participants using secondary data sources (i.e., data not collected in the course of the original trial, data identified from existing sources such as health administrative data electronic medical records or vital statistics) where the extension was not originally planned (e.g., where linkage to vital statistics to identify deaths occurring outside of the trial period was not explicitly mentioned in the original trial publication);

6) *Timeframe*: any;

7) *Publication*: any scientific reports of trial extensions, including abstracts.

We will exclude studies with the following characteristics:

1) extension of trials occurring within the year following the completion of the original trial as, arguably, trial extension was most likely within the authors' original intentions (even where not explicitly indicated); e.g., additional six months of follow-up of participants immediately following their completion of the original trial;

2) non-English language studies.

Data extraction and management

Two review authors will extract data from included studies using Covidence, systematic review software developed in partnership with the Cochrane Collaboration. Disagreements will be reached by discussion between the two review authors until a consensus is reached or will be resolved by a third author. Data and other information from studies will be extracted in a pre-defined form following the framework outlined in Table 1. The extraction form will be pilot-tested on a random sample of five selected studies, and refined accordingly.

We will attempt to contact authors for additional details when not otherwise reported in the published manuscript. Similarly, we will search the published literature databases listed above and the grey literature to identify other potential sources of relevant information related to the included post-trial linkage studies; e.g. conference proceedings where qualitative information, such as any practical challenges associated with the linkage, or the costs associated with the study, may be reported.

Table 1: Data extraction framework

Bibliometrics	Original Trial Characteristics	Follow-up Trial Characteristics
- Authors - Title - Year of publication - Publication source - Journal Impact (Low/High)	- Trial name - Country of origin - Original authors (differ from follow-up study's authors?) - Outcomes (primary and secondary) - Timeframe - Intervention applied - Potential/ realized clinical or policy implications - Funders	- Time since trial closure - Outcomes (primary and secondary) - Data sources for follow-up outcomes (e.g. health administrative, population registry) - Linkages fields and type linkage (probabilistic/ deterministic); where was linkage conducted (e.g. academic, gov't body, etc)? - Were the conclusions of the original trial altered? - Potential/ realized clinical or policy implications; e.g. evidence supporting or against current guidelines - Comments regarding ethics approval - Funders - Challenges, time requirements and costs associated with extension - Methodological issues (e.g. unadjusted time-varying confounding) - Stated reasons for trial extension (e.g. potential legacy effects)

Data analysis and synthesis

Given the nature of this review, we will report only descriptive information to provide a narrative synthesis of the findings from the included studies in this review. Specifically, our methodology will include quantitative (e.g., proportions) analyses to describe the types of trials for which extension studies have been conducted and summarize any practice implications or methodological challenges. For example, we will summarize whether the original findings of the trial were altered by additional follow-up and if the post-trial authors were able to report on new clinical outcomes identified through the linked administrative data sources.

CONCLUSION

To our knowledge this will be the first review of post-trial extension studies, specifically those using secondary population-based sources of outcome data, to identify the long-term outcomes in trial participants. The findings of this scoping review will help describe the growing field of post-trial extension studies using linked administrative and registry data and inform recommendations to support the further development of this field.

Authors' contributions: TF and DAH conceptualized the study and drafted the protocol. LP developed the detailed search strategy and critically revised the manuscript. ACT and SES provided expert scoping review methodological guidance. PJ, MZ, LL, MS and LCR offered conceptual, methodological and content feedback. All authors have read and approve the final manuscript.

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ANNEX 1: MEDLINE Search Strategy

Database: Ovid MEDLINE(R) <1946 to May Week 2 2016>,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 18, 2016>
Search Strategy:

1 (extension and trial).ti.
2 clinical trial.mp. [RCT filter - validated, highly sensitive]
3 clinical trial.pt.
4 random:.mp.
5 tu.xs.
6 or/2-5
7 ("2 year" adj "follow up").tw.
8 ("2$ year" adj "follow up").tw.
9 ("3 year" adj "follow up").tw.
10 ("3$ year" adj "follow up").tw.
11 ("4 year" adj "follow up").tw.
12 ("4$ year" adj "follow up").tw.
13 ("5 year" adj "follow up").tw.
14 ("5$ year" adj "follow up").tw.
15 ("6 year" adj "follow up").tw.
16 ("6$ year" adj "follow up").tw.
17 ("7 year" adj "follow up").tw.
18 ("7$ year" adj "follow up").tw.
19 ("8 year" adj "follow up").tw.
20 ("8$ year" adj "follow up").tw.
21 ("9 year" adj "follow up").tw.
22 ("9$ year" adj "follow up").tw.
23 ("1$ year" adj "follow up").tw.
24 ("long term" adj "follow up").tw.
25 *Follow-Up Studies/
26 *Longitudinal Studies/
27 (longitudinal adj stud$).tw.
28 (post adj trial?).tw.
29 (after adj trial?).tw.
30 (passive adj surveillance).tw.
31 or/7-30
32 Medical Records/
33 Health Records, Personal/
34 Medical Record Linkage/
35 Medical Records Systems, Computerized/
36 Electronic Health Records/
37 Health Information Exchange/
38 Nursing Records/
39 Records as Topic/
40 exp Hospital Information Systems/
41 exp Registries/
42 registry.tw.
43 registries.tw.
44 (data adj link$).tw.
45 (link$ adj2 data).tw.
46 (death adj certificate?).tw.
47 "vital stat$ data$".tw.
48 EHR.tw.
49 EMR.tw.
50 (medical adj record?).tw.
51 (health adj record?).tw.
52 (patient adj record?).tw.
53 (nursing adj record?).tw.
54 (national adj4 index).tw.
55 (national adj4 register?).tw.
56 (national adj4 data$).tw.
57 (administrative adj4 data$).tw.
58 (administrative adj4 record$).tw.
59 (population-based adj4 data$).tw.
60 or/32-59
61 6 and 31 and 60
62 1 or 61
63 exp Animals/ not (Humans/ and exp Animals/)
64 62 not 63
65 limit 64 to english language

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Andrea C. Tricco, PhD MSc [c d]	TriccoA@smh.ca
Sharon E. Straus, PhD MD MSc FRCP(C) [c]	Sharon.Straus@utoronto.ca
Peter Jüni, MD FESC [e f g]	Peter.Juni@utoronto.ca
Merrick Zwarenstein, MBBCh MSc PhD [h i]	Merrick.Zwarenstein@schulich.uwo.ca
Lisa M. Lix, PhD P.Stat MSc [j k]	Lisa.Lix@umanitoba.ca
Mark_Smith, MSc [k]	Mark.Smith@cpe.umanitoba.ca
Laura C. Rosella, PhD MHSc [d i l]	Laura.Rosella@utoronto.ca
David A. Henry, MB ChB MRCP FRCP [d g i]	David.Henry@utoronto.ca

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a Ontario Strategy for Patient-Oriented Research (SPOR) SUPPORT Unit, Toronto, ON, Canada;
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f Department of Medicine, University of Toronto, Toronto, ON, Canada;
g Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
h Department of Family Medicine, Schulich School of Medicine, University of Western Ontario, London, ON, Canada;
i Institute for Clinical Evaluative Sciences, ON, Canada
j Department of Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada
k Manitoba Centre for Health Policy, University of Manitoba, Winnipeg, MB, Canada
l Public Health Ontario, Toronto, ON, Canada

***Corresponding author contact details:**
Mailing Address: 6th Floor, 155 College St., Toronto, ON, Canada, M5T 3M6
Telephone: 416-978-8364

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INTRODUCTION

Randomized controlled trials (RCTs) are widely considered the gold standard for generating clinical evidence. High quality RCTs require considerable human and financial resources and, in some cases may require commitments spanning many years. Despite these investments, follow-up of patients typically ceases after the trial is completed as planned and the results have been released to inform clinical practice or regulatory decisions. At this point it can be said that a trial becomes 'dormant', as the data are no longer used for new research.

However, dormant trials offer considerable potential for new research, including reanalysis to confirm primary trial outcomes, analysis of new clinical outcomes and follow-up of participants to assess the potential long-term benefits and harms of interventions [1]. According to a scoping review by Ebrahim et al., re-analysis appears to be a fairly uncommon event [2]. Their review identified only 37 examples of trial re-analyses [2]. However, they did not look at additional uses of study data, such as post-trial extensions to assess long-term outcomes. Given growing demand for transparency in research, open data and data sharing, and tight fiscal budgets for research, the re-analysis, validation and re-activation of dormant trials is an attractive strategy to maximize the value gained from large investments in RCTs.

Arguably, the Diabetes Control and Complication Trial (DCCT) study group is a trailbreaker in the re-use of trial data and post-trial follow-up [3]. Since the completion of their original trial in the early 1990s, the group has been involved in over 200 analyses using data from the original DCCT or its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) [4]. Likewise, in recent years there have been several high-profile examples of trial extension studies, where authors follow participants for decades after trial closure using linkage to secondary data sources to assess potential long-term effects. For example, the 25-year follow-up of the Canadian National Breast Cancer Screening Study (CNBCSS) was published in 2014. Long-term follow-up was achieved by linkage to population-based cancer registry and vital statistics data [5]. This study found that annual mammography in women aged 40-59 did not reduce mortality from breast cancer when compared to usual care [5]. Another notable example is the 20-year follow-up of the West of Scotland Coronary Prevention study (WOSCOPS), which showed a lifetime benefit of improved survival and reduced cardiovascular disease following only five years of statin therapy [6].

These are only two prominent recent examples of trials that have been extended beyond the original planned term using secondary linked data sources; both of which provided important clinical findings. It is not clear, however, how many trials have been extended in this way. On the surface, this appears to be a fairly uncommon practice; particularly in relation to the number of high-impact RCTs that are completed each year. While some trials plan to study outcomes using secondary data sources as part of the original protocol, and some are designed as 'registry trials', few seem to have been extended as an independent exercise after the original study was completed.

There are several reasons why an investigator would be interested in conducting a post-trial extension study. Most obvious would be the desire to estimate the potential long-term benefits or adverse effects of an intervention [7]. Specifically, it is possible to map the accrual or loss of benefits over time with greater certainty. For instance, the extension of the WOSCOPS revealed a 'legacy' effect of a relatively short period of statin treatment, still visible after 20 years.[6] Post-trial extensions could also provide longer observations regarding the natural history of a disease among a

well-characterized control group, the persistence of adherence to therapy, and the patterns and effects of co-interventions introduced after trials end.

While highlighting the potential benefits of post-trial extension we acknowledge that it is uncertain whether the efforts and potential challenges will always be worthwhile, particularly in terms of novel findings that have important clinical or policy relevance. But the feasibility and low cost makes these exercises attractive. Advances in the availability of linkable population data sets and analytical capacity make this option more feasible than in the past, so we believe it will become an increasingly common activity. The relatively low cost of post-trial linkage studies is illustrated by WOSCOPS. The original trial cost approximately £20 million to complete, whereas the follow-up study was conducted for only £15,000 ($19,000; € 17500) [8].

It will be important for researchers to consider potential methodological, logistical and ethical challenges associated with post-trial extension studies. For instance, post-trial extensions are essentially observational, with management decisions influenced by practice guidelines rather than trial protocols. This introduces a potential for unmeasured time-varying confounding with threats to internal validity. This will be especially important in the case of interventions that are found to be effective and are rapidly adopted by control group members after trial termination. This could attenuate any long-term effects identified by the follow-up study, especially if cross-overs cannot be identified in the available secondary data sources and cannot be accounted for the analysis. Logistical challenges will include unavailability of data, storage in paper records and lack of linkable fields in the research data, for instance when records have been de-identified, but the linkage key is no longer available. Finally, it is unclear how research ethics boards will respond to requests to approve linkage of individual patient data when this was not specified in the original clinical trial consent form.

In the light of these considerations the principal objective of this scoping review is to quantify and characterize published post-trial extension studies, assess their value, and identify potential research gaps, logistical and ethical challenges associated with this approach. Upon completion of this review, we hope to report on several issues:

1. The number of published post-trial extension studies that have been completed using health administrative or registry data;
2. The types of outcomes assessed in these studies and how well they were detected (i.e., the type(s) of data and if there was any validation process);
3. The main challenges associated with conducting post-trial extensions (e.g., achieving data linkage, obtaining ethics approval, obtaining agreement from the original investigators, analytical challenges);
4. The extent to which the original published trial findings were altered with extended follow-up;
5. The costs and time involved in performing post-trial extensions; and
6. The likely clinical and policy implications of new information generated through post-trial extensions.

METHODS

We will undertake a scoping review to examine the literature covering post-trial extensions of RCTs using linked secondary data sources, such as health administrative or population registry data and electronic medical records, to ascertain long-term clinical outcomes of participants. The scoping

review methodology was selected to map the literature in this emerging area. [6,9-10]. Importantly, a scoping review will enable a broad examination of the nature, extent, and range of the research activity and help identify gaps in the current literature. Specifically, we will follow the standard methodological guidelines for conducting scoping studies, specifically those set out by the Joanna Briggs Institute handbook, and will report according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9-11].

Our protocol draws upon the framework outlined by Arksey and O'Malley [10], which outlines the following six -stage approach to conducting a scoping review: 1) developing the research question; 2) identifying all relevant studies; 3) selection of studies; 4) data extraction; 5) summary and reporting of results; and 6) consultation.

Study selection

Search strategy

The draft search strategy (for MEDLINE) was developed by an information specialist (LP), who was instrumental in maximizing its sensitivity and specificity and ensuring its feasibility. It will be assessed by a second information scientist according to the Peer Review of Electronic Search Strategies (PRESS) checklist [12] and will be refined as dictated by early results. The search strategy includes MeSH and text words related to randomized controlled trials, post-trial and long-term follow-up studies, and data linkage (including specific database types). Notably, since this is an emerging area of interest with little specialization, there are currently no dedicated indexing terms for this study type. Further, there is little standardization in how this study type is described. As such, the search strategy relies on a variety of non-standard search terms; e.g. "X-year follow-up".

The search strategy will be replicated in the EMBASE and the Cochrane Central Register of Controlled Trials databases. The search will be limited to English language articles; no other restrictions will be placed on the search strategy.

We will search for additional articles by using the Related Articles feature in PubMed for articles included in the scoping review and those deemed highly relevant by the core research team. This strategy was selected because previous work has shown that the Related Articles feature in PubMed can identify relevant studies with a relatively low screening burden of new records per review [13]. We decided to do this additional search as our initial scan identified several relevant studies that did not explicitly refer to data linkage in their abstract and would subsequently be missed by our search strategy. Finally, we will leverage the personal libraries and content knowledge of our clinical and epidemiological expert authors to identify any additional studies for inclusion.

Our MEDLINE search strategy can be found in **Appendix A**. Upon completion, the searches from each of the above databases will be documented and references imported into a reference management software program, where duplicates will be removed. All references will be stored and shared using a reference management software program (e.g. Reference Manager, Version 12).

Study selection

Prior to screening, we will conduct a calibration exercise with a sample of 50 retrieved citations to assess the reliability of our level 1 screening of title and abstracts. We will aim for agreement of at least 95% before beginning title and abstract screening. Subsequently, the abstracts and titles of all

retrieved references will be independently reviewed by two authors to identify potentially eligible studies for inclusion. Disagreements will be put forth for full-text review. The full text of all eligible citations will also be examined in detail by two independent reviewers. In cases of disagreement, consensus will be reached through discussion or be resolved by a third reviewer.

Studies will be eligible for inclusion if they satisfy all of the following criteria:

1) *Population:* any definable (human) patient population, including both children and adult populations. All countries and sub-populations will be included;

2) *Intervention*: any health-related intervention applied at the individual level, such as pharmaceutical interventions, lifestyle modification, screening practices, etc.;

3) *Outcomes* (primary or secondary): any health-related event, such as onset of disease, specific complications, health system outcome, or death that are considered likely to be detectable in administrative/registry data;

4) *Design*: limited to clinical trials that involve either individual or cluster randomization of individuals to an intervention or control group. We will include randomized crossover designs, adaptive designs, and factorial designs. We will not include quasi-experimental designs, self-controlled studies or those using interrupted time series analysis outside of a randomized controlled trial;

5) *Extension methods*: follow-up of trial participants using secondary data sources (i.e., data not collected in the course of the original trial, data identified from existing sources such as health administrative data electronic medical records or vital statistics) where the extension was not originally planned (e.g., where linkage to vital statistics to identify deaths occurring outside of the trial period was not explicitly mentioned in the original trial publication);

6) *Timeframe*: any;

7) *Publication*: any scientific reports of trial extensions, including abstracts.

We will exclude studies with the following characteristics:

1) extension of trials occurring within the year following the completion of the original trial as, arguably, trial extension was most likely within the authors' original intentions (even where not explicitly indicated); e.g., additional six months of follow-up of participants immediately following their completion of the original trial;

2) non-English language studies.

Data extraction and management

Two review authors will extract data from included studies using Covidence, systematic review software developed in partnership with the Cochrane Collaboration. Disagreements will be reached by discussion between the two review authors until a consensus is reached or will be resolved by a third author. Data and other information from studies will be extracted in a pre-defined form following the framework outlined in Table 1. The extraction form will be pilot-tested on a random sample of five selected studies, and refined accordingly.

We recognize that several of the outcomes of interest will not be determined by examination of numeric results (see Table 1) and will require a degree of interpretation and judgment. We will

perform a textual analysis to identify themes that correspond to these outcomes in a sample of the extended trials. We will map key words to these themes in the pilot sample of extended trials. We will use electronic searching to find the key words in all of the studies, but recognize that this will identify only potentially relevant sections of text and interpretation will still be needed. The number of studies will not be large, so we believe this will be manageable.

We will attempt to contact authors for additional details when not otherwise reported in the published manuscript. Similarly, we will search the published literature databases listed above and the grey literature to identify other potential sources of relevant information related to the included post-trial linkage studies; e.g. conference proceedings where qualitative information, such as any practical challenges associated with the linkage, or the costs associated with the study, may be reported.

Table 1: Data extraction framework

Bibliometrics	Original Trial Characteristics	Follow-up Trial Characteristics
- Authors - Title - Year of publication - Publication source - Journal Impact (Low/High)	- Trial name - Country of origin - Original authors (differ from follow-up study's authors?) - Outcomes (primary and secondary) - Timeframe - Intervention applied - Potential/ realized clinical or policy implications - Funders	- Time since trial closure - Data sources for follow-up outcomes (e.g. health administrative, population registry, electronic medical records - EMR). - Linkages fields and type linkage (probabilistic/ deterministic); where was linkage conducted (e.g. academic, gov't body, etc)? Outcomes (primary and secondary); identification of extended trial outcomes: structured data (eg claims data); unstructured data - information contained in text (eg. EMR) or other documents; technique used for extracting information: manual, text mining - Were the conclusions of the original trial altered? - Potential/ realized clinical or policy implications; e.g. evidence supporting or against current guidelines - Comments regarding ethics approval - Funders - Challenges, time requirements and costs associated with extension - Methodological issues (e.g. unadjusted time-varying confounding) - Stated reasons for trial extension (e.g. long-term treatment effects, potential 'legacy' effects)

Data analysis and synthesis

Given the nature of this review, we will report only descriptive information to provide a narrative synthesis of the findings from the included studies in this review. Specifically, our methodology will include quantitative (e.g., proportions) analyses to describe the types of trials for which extension studies have been conducted and summarize any practice implications or methodological challenges. For example, we will summarize whether the original findings of the trial were altered by additional follow-up and if the post-trial authors were able to report on new clinical outcomes identified through the linked administrative data sources.

CONCLUSION

To our knowledge this will be the first review of post-trial extension studies, specifically those using secondary population-based sources of outcome data, to identify the long-term outcomes in trial participants. The findings of this scoping review will help describe the growing field of post-trial extension studies using linked administrative and registry data and inform recommendations to support the further development of this field.

Authors' contributions: TF and DAH conceptualized the study and drafted the protocol. LP developed the detailed search strategy and critically revised the manuscript. ACT and SES provided expert scoping review methodological guidance. PJ, MZ, LL, MS and LCR offered conceptual, methodological and content feedback. All authors have read and approve the final manuscript.

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Competing interests statement: The authors have no relevant conflicts of interest to report.

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ANNEX 1: MEDLINE Search Strategy

Database: Ovid MEDLINE(R) <1946 to May Week 2 2016>,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 18, 2016>
Search Strategy:

1 (extension and trial).ti.
2 clinical trial.mp. [RCT filter - validated, highly sensitive]
3 clinical trial.pt.
4 random:.mp.
5 tu.xs.
6 or/2-5
7 ("2 year" adj "follow up").tw.
8 ("2$ year" adj "follow up").tw.
9 ("3 year" adj "follow up").tw.
10 ("3$ year" adj "follow up").tw.
11 ("4 year" adj "follow up").tw.
12 ("4$ year" adj "follow up").tw.
13 ("5 year" adj "follow up").tw.
14 ("5$ year" adj "follow up").tw.
15 ("6 year" adj "follow up").tw.
16 ("6$ year" adj "follow up").tw.
17 ("7 year" adj "follow up").tw.
18 ("7$ year" adj "follow up").tw.
19 ("8 year" adj "follow up").tw.
20 ("8$ year" adj "follow up").tw.
21 ("9 year" adj "follow up").tw.
22 ("9$ year" adj "follow up").tw.
23 ("1$ year" adj "follow up").tw.
24 ("long term" adj "follow up").tw.
25 *Follow-Up Studies/
26 *Longitudinal Studies/
27 (longitudinal adj stud$).tw.
28 (post adj trial?).tw.
29 (after adj trial?).tw.
30 (passive adj surveillance).tw.
31 or/7-30
32 Medical Records/
33 Health Records, Personal/
34 Medical Record Linkage/
35 Medical Records Systems, Computerized/
36 Electronic Health Records/
37 Health Information Exchange/
38 Nursing Records/
39 Records as Topic/
40 exp Hospital Information Systems/
41 exp Registries/
42 registry.tw.
43 registries.tw.
44 (data adj link$).tw.
45 (link$ adj2 data).tw.
46 (death adj certificate?).tw.
47 "vital stat$ data$".tw.
48 EHR.tw.
49 EMR.tw.
50 (medical adj record?).tw.
51 (health adj record?).tw.
52 (patient adj record?).tw.
53 (nursing adj record?).tw.
54 (national adj4 index).tw.
55 (national adj4 register?).tw.
56 (national adj4 data$).tw.
57 (administrative adj4 data$).tw.
58 (administrative adj4 record$).tw.
59 (population-based adj4 data$).tw.
60 or/32-59
61 6 and 31 and 60
62 1 or 61
63 exp Animals/ not (Humans/ and exp Animals/)
64 62 not 63
65 limit 64 to english language

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6 or/2-5
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8 ("2$ year" adj "follow up").tw.
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10 ("3$ year" adj "follow up").tw.
11 ("4 year" adj "follow up").tw.
12 ("4$ year" adj "follow up").tw.
13 ("5 year" adj "follow up").tw.
14 ("5$ year" adj "follow up").tw.
15 ("6 year" adj "follow up").tw.
16 ("6$ year" adj "follow up").tw.
17 ("7 year" adj "follow up").tw.
18 ("7$ year" adj "follow up").tw.
19 ("8 year" adj "follow up").tw.
20 ("8$ year" adj "follow up").tw.
21 ("9 year" adj "follow up").tw.
22 ("9$ year" adj "follow up").tw.
23 ("1$ year" adj "follow up").tw.
24 ("long term" adj "follow up").tw.
25 *Follow-Up Studies/
26 *Longitudinal Studies/
27 (longitudinal adj stud$).tw.
28 (post adj trial?).tw.
29 (after adj trial?).tw.
30 (passive adj surveillance).tw.
31 or/7-30
32 Medical Records/
33 Health Records, Personal/
34 Medical Record Linkage/
35 Medical Records Systems, Computerized/
36 Electronic Health Records/
37 Health Information Exchange/
38 Nursing Records/
39 Records as Topic/
40 exp Hospital Information Systems/
41 exp Registries/
42 registry.tw.
43 registries.tw.
44 (data adj link$).tw.
45 (link$ adj2 data).tw.
46 (death adj certificate?).tw.
47 "vital stat$ data$".tw.
48 EHR.tw.
49 EMR.tw.
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51 (health adj record?).tw.
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54 (national adj4 index).tw.
55 (national adj4 register?).tw.
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57 (administrative adj4 data$).tw.
58 (administrative adj4 record$).tw.
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61 6 and 31 and 60
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