資料7

本試験の内容と目的

- お子さんの繰り返す急性中耳炎に悩んでおられる皆様に対し、現在全国でおこなわれております臨床試験についてご案内致します。詳細は「説明文書」をご覧下さい。

- 近年、0才～3才ごろまでの小さなお子さんに、急性中耳炎が繰り返しおこる「反復性中耳炎」が全国的に増加し、社会的問題となっています。

  - 原因の一つとして、薬が効きにくくなった「薬剤耐性菌」の問題も挙げられています。そしてまた、お子さんの身体の構造や免疫能が大人に比べて発育途上であることも、理由の一つとする考え方があります。

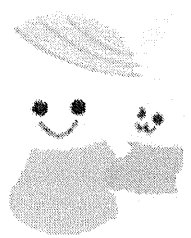
- 中耳炎の反復を予防する方法として、鼻の処置や鼻かみで鼻汁をこまめに除去することや、「鼓膜チューブ挿入術」をおこない、チューブを通して耳を長期間よい状態に保つ方法などが挙げられます。

- その他の方法として、漢方薬の一種である十全大補湯の可能性が検討されています。十全大補湯は厚生労働省の認める医薬品の一つですが、反復性中耳炎に対してこのお薬が本当に「有効」でかつ「安全」であるかどうか、今のところまだ、はっきりとわかっていません。また、その有効性を疑問視する考え方もあります。

- この試験は、反復性中耳炎に対する十全大補湯の効果の有無を、科学的に評価することを目的とした試験です。なお、この試験は厚生労働省が認可しており、その協力のもとにおこなわれます。

- もちろん、風邪や中耳炎をふくめたお子さんの病気について、今までどおり、精一杯の治療をおこないます。その上で、半分の方には治療を継続し、残りの半分の方にはさらに十全大補湯を服用してもらうことになります。この振り分けについては、中央登録専門部署で、コンピュータによって偏りなく公正に決定されます。

- つまり、振り分けについては、主治医の先生方も関与できない方針をとらせて頂いております。従いまして治療内容などをすべてご説明した後で、十全大補湯を服用せずに現在の治療を継続するグループに参加していただく可能性もあります。



✧ **お子さんに対する精一杯の治療をおこないながら、皆さんとともに、感染症に対する、よりよい治療法を求めていきたいと考えています。**

✧ **ご理解とご協力をいただけますよう、どうぞよろしくお願い致します。**

小児反復性中耳炎に関する臨床試験のお知らせ

- 現在当院では、厚生労働省の認可・支援のもと、小児反復性中耳炎に関する全国多施設共同臨床試験をおこなっています。
- ご協力いただける方、ご興味のある方は、担当医師までお問い合わせください。

【主な参加基準】

- ◆ 半年間に3回以上、または1年間に4回以上の急性中耳炎を繰り返しているお子さん
- ◆ 年齢：6か月以上4歳未満

※「臨床試験」とは

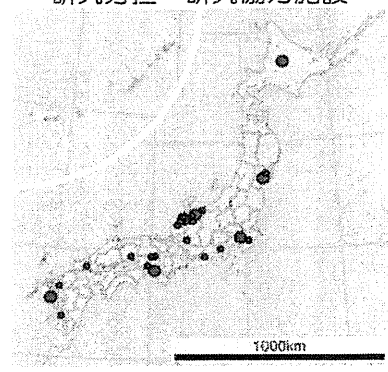
病院で患者さまが受けておられる治療は、現時点で最も良いと科学的に評価されている治療が中心になっています。

臨床試験とは、新しい治療法がこれまでの治療より優れているかどうか、更によい治療法といえるかどうかを科学的に調査するためにおこなわれる試験のことです。

厚生労働省
臨床研究・予防・治療技術開発研究事業

研究代表
金沢大学　耳鼻咽喉科・頭頸部外科

研究分担・研究協力施設



研究分担・研究協力施設（50音順）

旭川医科大学　耳鼻咽喉科・頭頸部外科
医療法人社団和康会 河合医院
いわなが耳鼻咽喉科クリニック
宇野耳鼻咽喉科クリニック
金沢社会保険病院　耳鼻咽喉科
上出耳鼻咽喉科医院
かみで耳鼻咽喉科クリニック
黒部市民病院　耳鼻咽喉科
甲南病院 耳鼻咽喉科
耳鼻咽喉科形成美容外科　香山医院
耳鼻咽喉科　ののはなクリニック
真生会富山病院　耳鼻咽喉科
せんだい耳鼻咽喉科
千葉県こども病院　耳鼻咽喉科
東京医科歯科大学 耳鼻咽喉科
東北大学　耳鼻咽喉科・頭頸部外科
東北労災病院　耳鼻咽喉科
富山大学　耳鼻咽喉科・頭頸部外科
長崎大学　耳鼻咽喉科・頭頸部外科
兵庫県立こども病院　耳鼻咽喉科
ほりかわクリニック
ほんま耳鼻咽喉科
松原耳鼻いんこう科医院
和歌山県立医科大学　耳鼻咽喉科・頭頸部外科

RESEARCH METHODS & REPORTING

CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

Kenneth F Schulz,[1] Douglas G Altman,[2] David Moher,[3] for the CONSORT Group

EDITORIAL by Antes
RESEARCH, p 697

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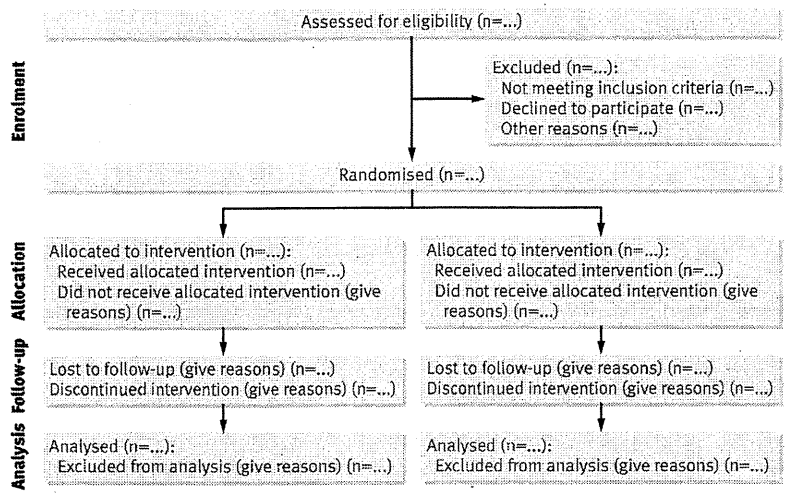
The CONSORT statement is used worldwide to improve the reporting of randomised controlled trials. **Kenneth Schulz and colleagues** describe the latest version, CONSORT 2010, which updates the reporting guideline based on new methodological evidence and accumulating experience

Randomised controlled trials, when appropriately designed, conducted, and reported, represent the gold standard in evaluating healthcare interventions. However, randomised trials can yield biased results if they lack methodological rigour.[1] To assess a trial accurately, readers of a published report need complete, clear, and transparent information on its methodology and findings. Unfortunately, attempted assessments frequently fail because authors of many trial reports neglect to provide lucid and complete descriptions of that critical information.[2-4]

That lack of adequate reporting fuelled the development of the original CONSORT (Consolidated Standards of Reporting Trials) statement in 1996[5] and its revision five years later.[6-8] While those statements improved the reporting quality for some randomised controlled trials,[9 10] many trial reports still remain inadequate.[2] Furthermore, new methodological evidence and additional experience has accumulated since the last revision in 2001. Consequently, we organised a CONSORT Group meeting to update the 2001 statement.[6-8] We introduce here the result of that process, CONSORT 2010.



Flow diagram of the progress through the phases of a parallel randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis)

Intent of CONSORT 2010

The CONSORT 2010 Statement is this paper including the 25 item checklist in the table and the flow diagram. It provides guidance for reporting all randomised controlled trials, but focuses on the most common design type—individually randomised, two group, parallel trials. Other trial designs, such as cluster randomised trials and non-inferiority trials, require varying amounts of additional information. CONSORT extensions for these designs,[11 12] and other CONSORT products, can be found through the CONSORT website (www.consort-statement.org). Along with the CONSORT statement, we have updated the explanation and elaboration article,[13] which explains the inclusion of each checklist item, provides methodological background, and gives published examples of transparent reporting.

Diligent adherence by authors to the checklist items facilitates clarity, completeness, and transparency of reporting. Explicit descriptions, not ambiguity or omission, best serve the interests of all readers. Note that the CONSORT 2010 Statement does not include recommendations for designing, conducting, and analysing trials. It solely addresses the reporting of what was done and what was found.

Nevertheless, CONSORT does indirectly affect design and conduct. Transparent reporting reveals deficiencies in research if they exist. Thus, investigators who conduct inadequate trials, but who must transparently report, should not be able to pass through the publication process without revelation of their trial's inadequacies. That emerging reality should provide impetus to improved trial design and conduct in the future, a secondary indirect goal of our work. Moreover, CONSORT can help researchers in designing their trial.

Background to CONSORT

Efforts to improve the reporting of randomised controlled trials accelerated in the mid-1990s, spurred partly by methodological research. Researchers had shown for many years that authors reported such trials poorly, and empirical evidence began to accumulate that some poorly conducted or poorly reported aspects of trials were associated with bias.[14] Two initiatives aimed at developing reporting guidelines culminated in one of us (DM) and Drummond Rennie organising the first CONSORT statement in 1996.[5]

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item
Title and abstract		
	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts[21 31])
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[28])
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration[13] for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials,[11] non-inferiority and equivalence trials,[12] non-pharmacological treatments,[32] herbal interventions,[33] and pragmatic trials.[34] Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Further methodologi cal research on similar topics reinforced earlier findings[15] and fed into the revision of 2001.[6-8] Subsequently, the expanding body of methodological research informed the refinement of CONSORT 2010. More than 700 studies comprise the CONSORT database (located on the CONSORT website), which provides the empirical evidence to underpin the CONSORT initiative.

Indeed, CONSORT Group members continually monitor the literature. Information gleaned from these efforts provides an evidence base on which to update the CONSORT statement. We add, drop, or modify items based on that evidence and the recommendations of the CONSORT Group, an international and eclectic group of clinical trialists, statisticians, epidemiologists, and biomedical editors. The CONSORT Executive (KFS, DGA, DM) strives for a balance of established and emerging researchers. The membership of the group is dynamic. As our work expands in response to emerging projects and needed expertise, we invite new members to contribute. As such, CONSORT continually assimilates new ideas and perspectives. That process informs the continually evolving CONSORT statement.

Over time, CONSORT has garnered much support. More than 400 journals, published around the world and in many languages, have explicitly supported the CONSORT

statement. Many other healthcare journals support it without our knowledge. Moreover, thousands more have implicitly supported it with the endorsement of the CONSORT statement by the International Committee of Medical Journal Editors (www.icmje.org). Other prominent editorial groups, the Council of Science Editors and the World Association of Medical Editors, officially support CONSORT. That support seems warranted: when used by authors and journals, CONSORT seems to improve reporting.[9]

Development of CONSORT 2010

Thirty one members of the CONSORT 2010 Group met in Montebello, Canada, in January 2007 to update the 2001 CONSORT statement. In addition to the accumulating evidence relating to existing checklist items, several new issues had come to prominence since 2001. Some participants were given primary responsibility for aggregating and synthesising the relevant evidence on a particular checklist item of interest. Based on that evidence, the group deliberated the value of each item. As in prior CONSORT versions, we kept only those items deemed absolutely fundamental to reporting a randomised controlled trial. Moreover, an item may be fundamental to a trial but not included, such as approval by an institutional ethical review board, because funding bodies strictly enforce ethical review and medical journals usually address reporting ethical review in their instructions for authors. Other items may seem desirable, such as reporting on whether on-site monitoring was done, but a lack of empirical evidence or any consensus on their value cautions against inclusion at this point. The CONSORT 2010 Statement thus addresses the minimum criteria, although that should not deter authors from including other information if they consider it important.

After the meeting, the CONSORT Executive convened teleconferences and meetings to revise the checklist. After seven major iterations, a revised checklist was distributed to the larger group for feedback. With that feedback, the executive met twice in person to consider all the comments and to produce a penultimate version. That served as the basis for writing the first draft of this paper, which was then distributed to the group for feedback. After consideration of their comments, the executive finalised the statement.

The CONSORT Executive then drafted an updated explanation and elaboration manuscript, with assistance from other members of the larger group. The substance of the 2007 CONSORT meeting provided the material for the update. The updated explanation and elaboration manuscript was distributed to the entire group for additions, deletions, and changes. That final iterative process converged to the CONSORT 2010 Explanation and Elaboration.[13]

Box 1 | Noteworthy general changes in CONSORT 2010 Statement

- We simplified and clarified the wording, such as in items 1, 8, 10, 13, 15, 16, 18, 19, and 21
- We improved consistency of style across the items by removing the imperative verbs that were in the 2001 version
- We enhanced specificity of appraisal by breaking some items into sub-items. Many journals expect authors to complete a CONSORT checklist indicating where in the manuscript the items have been addressed. Experience with the checklist noted pragmatic difficulties when an item comprised multiple elements. For example, item 4 addresses eligibility of participants and the settings and locations of data collection. With the 2001 version, an author could provide a page number for that item on the checklist, but might have reported only eligibility in the paper, for example, and not reported the settings and locations. CONSORT 2010 relieves obfuscations and forces authors to provide page numbers in the checklist for both eligibility and settings

Changes in CONSORT 2010

The revision process resulted in evolutionary, not revolutionary, changes to the checklist (table), and the flow diagram was not modified except for one word (figure). Moreover, because other reporting guidelines augmenting the checklist refer to item numbers, we kept the existing items under their previous item numbers except for some renumbering of items 2 to 5. We added additional items either as a sub-item under an existing item, an entirely new item number at the end of the checklist, or (with item 3) an interjected item into a renumbered segment. We have summarised the noteworthy general changes in box 1 and specific changes in box 2. The CONSORT website contains a side by side comparison of the 2001 and 2010 versions.

Implications and limitations

We developed CONSORT 2010 to assist authors in writing reports of randomised controlled trials, editors and peer reviewers in reviewing manuscripts for publication, and readers in critically appraising published articles. The CONSORT 2010 Explanation and Elaboration provides elucidation and context to the checklist items. We strongly recommend using the explanation and elaboration in conjunction with the checklist to foster complete, clear, and transparent reporting and aid appraisal of published trial reports.

CONSORT 2010 focuses predominantly on the two group, parallel randomised controlled trial, which accounts for over half of trials in the literature.[2] Most of the items from the CONSORT 2010 Statement, however, pertain to all types of randomised trials. Nevertheless, some types of trials or trial situations dictate the need for additional information in the trial report. When in doubt, authors, editors, and readers should consult the CONSORT website for any CONSORT extensions, expansions (amplifications), implementations, or other guidance that may be relevant.

The evidence based approach we have used for CONSORT also served as a model for development of other reporting guidelines, such as for reporting systematic reviews and meta-analyses of studies evaluating interventions,[16] diagnostic studies,[17] and observational studies.[18] The explicit goal of all these initiatives is to improve reporting. The Enhancing the Quality and Transparency of Health Research (EQUATOR) Network will facilitate development of reporting guidelines and help disseminate the guidelines: www.equator-network.org provides information on all reporting guidelines in health research.

With CONSORT 2010, we again intentionally declined to produce a rigid structure for the reporting of randomised trials. Indeed, SORT[19] tried a rigid format, and it failed in a pilot run with an editor and authors.[20] Consequently, the format of articles should abide by journal style, editorial directions, the traditions of the research field addressed, and, where possible, author preferences. We do not wish to standardise the structure of reporting. Authors should simply address checklist items somewhere in the article, with ample detail and lucidity. That stated, we think that manuscripts benefit from frequent subheadings within the major sections, especially the methods and results sections.

Box 2 | Noteworthy specific changes in CONSORT 2010 Statement

- *Item 1b (title and abstract)*—We added a sub-item on providing a structured summary of trial design, methods, results, and conclusions and referenced the CONSORT for abstracts article[21]
- *Item 2b (introduction)*—We added a new sub-item (formerly item 5 in CONSORT 2001) on "Specific objectives or hypotheses"
- *Item 3a (trial design)*—We added a new item including this sub-item to clarify the basic trial design (such as parallel group, crossover, cluster) and the allocation ratio
- *Item 3b (trial design)*—We added a new sub-item that addresses any important changes to methods after trial commencement, with a discussion of reasons
- *Item 4 (participants)*—Formerly item 3 in CONSORT 2001
- *Item 5 (interventions)*—Formerly item 4 in CONSORT 2001. We encouraged greater specificity by stating that descriptions of interventions should include "sufficient details to allow replication"[3]
- *Item 6 (outcomes)*—We added a sub-item on identifying any changes to the primary and secondary outcome (endpoint) measures after the trial started. This followed from empirical evidence that authors frequently provide analyses of outcomes in their published papers that were not the prespecified primary and secondary outcomes in their protocols, while ignoring their prespecified outcomes (that is, selective outcome reporting).[4 22] We eliminated text on any methods used to enhance the quality of measurements
- *Item 9 (allocation concealment mechanism)*—We reworded this to include mechanism in both the report topic and the descriptor to reinforce that authors should report the actual steps taken to ensure allocation concealment rather than simply report imprecise, perhaps banal, assurances of concealment
- *Item 11 (blinding)*—We added the specification of how blinding was done and, if relevant, a description of the similarity of interventions and procedures. We also eliminated text on "how the success of blinding (masking) was assessed" because of a lack of empirical evidence supporting the practice as well as theoretical concerns about the validity of any such assessment[23 24]
- *Item 12a (statistical methods)*—We added that statistical methods should also be provided for analysis of secondary outcomes
- *Sub-item 14b (recruitment)*—Based on empirical research, we added a sub-item on "Why the trial ended or was stopped"[25]
- *Item 15 (baseline data)*—We specified "A table" to clarify that baseline and clinical characteristics of each group are most clearly expressed in a table
- *Item 16 (numbers analysed)*—We replaced mention of "intention to treat" analysis, a widely misused term, by a more explicit request for information about retaining participants in their original assigned groups[26]
- *Sub-item 17b (outcomes and estimation)*—For appropriate clinical interpretability, prevailing experience suggested the addition of "For binary outcomes, presentation of both relative and absolute effect sizes is recommended"[27]
- *Item 19 (harms)*—We included a reference to the CONSORT paper on harms[28]
- *Item 20 (limitations)*—We changed the topic from "Interpretation" and supplanted the prior text with a sentence focusing on the reporting of sources of potential bias and imprecision
- *Item 22 (interpretation)*—We changed the topic from "Overall evidence." Indeed, we understand that authors should be allowed leeway for interpretation under this nebulous heading. However, the CONSORT Group expressed concerns that conclusions in papers frequently misrepresented the actual analytical results and that harms were ignored or marginalised. Therefore, we changed the checklist item to include the concepts of results matching interpretations and of benefits being balanced with harms
- *Item 23 (registration)*—We added a new item on trial registration. Empirical evidence supports the need for trial registration, and recent requirements by journal editors have fostered compliance[29]
- *Item 24 (protocol)*—We added a new item on availability of the trial protocol. Empirical evidence suggests that authors often ignore, in the conduct and reporting of their trial, what they stated in the protocol.[4 22] Hence, availability of the protocol can instigate adherence to the protocol before publication and facilitate assessment of adherence after publication
- *Item 25 (funding)*—We added a new item on funding. Empirical evidence points toward funding source sometimes being associated with estimated treatment effects[30]

CONSORT urges completeness, clarity, and transparency of reporting, which simply reflects the actual trial design and conduct. However, as a potential drawback, a reporting guideline might encourage some authors to report fictitiously the information suggested by the guidance rather than what was actually done. Authors, peer reviewers, and editors should vigilantly guard against that potential drawback and refer, for example, to trial protocols, to information on trial registers, and to regulatory agency websites. Moreover, the CONSORT 2010 Statement does not include recommendations for designing and conducting randomised trials. The items should elicit clear pronouncements of how and what the authors did, but do not contain any judgments on how and what the authors should have done. Thus, CONSORT 2010 is not intended as an instrument to evaluate the quality of a trial. Nor is it appropriate to use the checklist to construct a "quality score."

Nevertheless, we suggest that researchers begin trials with their end publication in mind. Poor reporting allows authors, intentionally or inadvertently, to escape scrutiny of any weak aspects of their trials. However, with wide adoption of CONSORT by journals and editorial groups, most authors should have to report transparently all important aspects of their trial. The ensuing scrutiny rewards well conducted trials and penalises poorly conducted trials. Thus, investigators should understand the CONSORT 2010 reporting guidelines before starting a trial as a further incentive to design and conduct their trials according to rigorous standards.

CONSORT 2010 supplants the prior version published in 2001. Any support for the earlier version accumulated from journals or editorial groups will automatically extend to this newer version, unless specifically requested otherwise. Journals that do not currently support CONSORT may do so by registering on the CONSORT website. If a journal supports or endorses CONSORT 2010, it should cite one of the original versions of CONSORT 2010, the CONSORT 2010 Explanation and Elaboration, and the CONSORT website in their "Instructions to authors." We suggest that authors who wish to cite CONSORT should cite this or another of the original journal versions of CONSORT 2010 Statement, and, if appropriate, the CONSORT 2010 Explanation and Elaboration.[13] All CONSORT material can be accessed through the original publishing journals or the CONSORT website. Groups or individuals who desire to translate the CONSORT 2010 Statement into

bmj.com: recent Research Methods & Reporting articles

- Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design (2010;340:c1066)
- Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes (2010;340:b5087)
- Economic impact of disease and injury: counting what matters (2010;340:c924)
- The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews (2010;340:c365)
- Meta-analysis of individual participant data: rationale, conduct, and reporting (2010;340:c221)

other languages should first consult the CONSORT policy statement on the website.

We emphasise that CONSORT 2010 represents an evolving guideline. It requires perpetual reappraisal and, if necessary, modifications. In the future we will further revise the CONSORT material considering comments, criticisms, experiences, and accumulating new evidence. We invite readers to submit recommendations via the CONSORT website.

Author contributions: KFS, DM, and DGA participated in meetings and regular conference calls, planned the CONSORT 2007 meeting at Montebello, developed the agenda, prepared background research, identified and invited participants, contributed to the CONSORT meeting, drafted the manuscript, and, after critical review by the CONSORT Group, finalised the text of the manuscript. Members of the CONSORT Group attended the meeting, except for those noted below, and provided input on and review of the revised checklist and text of this article. Some members also prepared background material.

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資料9

統計解析計画書

小児反復性中耳炎に対する漢方薬(十全大補湯)に関するランダム化比較試験

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なお、*印の箇所は優先解析する。

目　次

1. 緒言

難治性・反復性感染症に対し、現行の対感染症治療を補助しその効果を増強する新しい治療法の開発が必要である。近年，漢方薬に関する基礎・臨床研究が進展し、さまざまな有益な効果が証明されてきている。補剤とは病後の状態など体内の生命活動活性の低下した状態を補い、消化吸収能力の改善により食欲増進とともに栄養状態を改善させることにより、身体の恒常性を回復させる一群の漢方薬を指す。代表的補剤である十全大補湯（以下 TJ-48)が小児急性中耳炎の治療に効果のあることが小規模の臨床研究からも明らかになりつつある。また、小児急性中耳炎診療ガイドライン（2009 年版）の「反復性中耳炎の治療」の項に、十全大補湯の投与の報告事例が引用されている。そこで今回，小児反復性中耳炎における TJ-48 の有用性を科学的に検討すべく多施設共同研究計画を立案した。

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2. 試験の目的

小児反復性中耳炎を対象として、ツムラ十全大補湯エキス顆粒による急性中耳炎(AOM)の再発抑制効果、免疫状態及び栄養状態の改善効果などを検証することが本試験の目的である。

3. 試験デザイン

3.1 試験方法

Randomized, Parallel-group, Open-label, Non-Kampo controlled Trial

ツムラ十全大補湯エキス顆粒を投与するか（投与群)、投与しないか（非投与群）をランダム（無作為）に割り付ける。全体で 100 例の小児反復性中耳炎患者を、ランダムに十全大補湯の投与群あるいは非投与群へ割り付け、12 週間観察する臨床試験である。

3.2 ランダム化の手法

市販ソフト「割付君」を用いて、Ｗｅｂシステムにより登録割り付けを行う。手法としてはPermuted block design を用いた。

3.3 十全大補湯の投与量

TJ-48 エキス顆粒

0.1～0.25g/kg/日　分 2

3.4 目標症例数

全体で 100 症例

3.5 投与期間

12 週間

4. 統計解析について

統計解析計画書を作成するに際しては、CONSORT2010 声明(Ann Intern Med 2010; 152: 726-732.) を参照した。

統計解析の有意水準は両側 P<0.05 と設定するが、正確な P 値を表示する。また、推定値の信頼区間の係数は 95%とする。統計解析には SAS Version 9.2 を用いる。

5. 解析対象集団

解析対象集団は、ランダム割り付けされた全症例の中で、データの回収がなされなかった症例を除外した症例で定義する。

6. データ範囲の許容範囲

4 週時 (1～4 週)、8 週時 (5～8 週)、12 週時 (9～12 週) のデータは、日付を確認し、適時点として採用するものとする。

7. 患者背景の解析*

投与群と非投与群ごとに、下記に示す項目を対比して表示する。

・年齢(平均±標準偏差、及び中央値・範囲・四分位範囲)
・性別 (男女別の人数と割合)
・身長(平均±標準偏差、及び中央値・範囲・四分位範囲)
・体重(平均±標準偏差、及び中央値・範囲・四分位範囲)
・保育園・幼稚園などへの通園状況 (人数と割合)
・兄姉の保育園などへの通園状況 (人数と割合)
・哺乳状況 (人数と割合)
・家族の喫煙 Tobacco smoke exposure (人数と割合)
・鼻副鼻腔炎 (人数と割合)
・アレルギー性鼻炎 (人数と割合)
・気管支喘息 (人数と割合)
・アトピー性皮膚炎 (人数と割合)
・「証」に関する事項 (人数と割合)
  ・活気、体温、汗、皮膚、顔色、嘔吐、下痢、食欲、咳
  [以上、問診票より引用]
・開始前の 1 ヶ月当たりの中耳炎の罹患回数 (平均±標準偏差、

及び中央値・範囲・四分位範囲）
［問診票 p. 2 及び主治医経過録 p. 2 より引用］

8.　有効性の解析

一次エンドポイント：

1か月当たりの中耳炎の平均罹患回数

［主治医経過録より引用］

8.1 1か月当たりの中耳炎の平均罹患回数に関する比較*

1ヶ月当たりの中耳炎の平均罹患回数について、投与群と非投与群ごとに平均±標準偏差、及び、中央値・範囲・四分位範囲を算出する。群間の違いは、t 検定及び Wilcoxon rank-sum test で比較する。

8.2 1か月当たりの中耳炎の平均罹患回数の前後差に関する比較*

開始前の1ヶ月当たりの中耳炎の罹患回数と、開始後の 1 か月当たりの中耳炎の平均罹患回数の差（開始後－開始前）を取り、それに関する 2 群比較を行う。両群ごとに平均±標準偏差、及び、中央値・範囲・四分位範囲を算出し、t 検定及び Wilcoxon rank-sum test を行う。また、（開始後－開始前）÷開始前×100%＝変化率と定義し、両群ごとに変化率の平均±標準偏差、及び、中央値・範囲・四分位範囲も算出する。

二次エンドポイント：

- 1か月当たりの上気道炎の平均罹患回数
- 1か月当たりの抗菌薬の平均投与回数
- 鼓膜チューブ挿入（12 週中）
- 中耳炎スコア

  耳痛・発熱・啼泣/不機嫌・鼓膜発赤・耳漏・光錐より

  ［主治医経過録より引用］
- 1か月当たりの各症状の平均有症日数
- 栄養状態（12 週時）
- 貧血・血液状態（12 週時）
- 免疫状態（12 週時）

  ［主治医経過録, p. 18 より引用］

8.3 1か月当たりの上気道炎の平均罹患回数に関する比較

1ヵ月当たりの上気道炎の平均罹患回数について、投与群と非投与群ご

とに平均±標準偏差、及び、中央値・範囲・四分位範囲を算出するし、t検定及びWilcoxon rank-sum testで群間比較する。

8.4　1か月当たりの抗菌薬の投与日数に関する比較*

1ヵ月当たりの抗菌薬の平均投与日数に関して、投与群と非投与群ごとに平均±標準偏差、及び、中央値・範囲・四分位範囲）を算出し、t検定及びWilcoxon rank-sum testで群間比較する。

8.5　鼓膜チューブ挿入に関する比較*

鼓膜チューブ挿入の有無については、投与群と非投与群ごとに有無の人数と割合を算出する。挿入率の2群比較は、Pearson's chi-square test及びFisher's exact testで検定する。

また、鼓膜チューブ挿入までの期間に関して、投与群と非投与群ごとにKaplan-Meier plot(付録A)を描き、Log-rank testを実施する。

8.6　中耳炎スコアに関する比較*

中耳炎が起こるたびに中耳炎スコアが調査されているので、各症例につき中耳炎スコアの合計点を求め、それを中耳炎の罹患回数で割った値に関し、投与群と非投与群ごとに平均±標準偏差、及び、中央値・範囲・四分位範囲を算出する。また、t検定及びWilcoxon rank-sum testで比較する。

8.7　1か月当たりの各症状の平均有症日数に関する比較

患者日誌から算出した「発熱日数、耳痛、不機嫌、耳漏、膿性鼻漏、水様性鼻漏、咳」について、1か月当たりの平均有症日数換に関し、投与群と非投与群ごとにその平均±標準偏差、及び中央値・範囲・四分位範囲を算出する。また、t検定及びWilcoxon rank-sum testで比較する。

8.8　12週時の栄養状態に関する比較

栄養状態については、12週時のアルブミン値及びカウプ指数（=体重g÷身長cm^2×10）で評価する。投与群と非投与群ごとに平均±標準偏差、及び、中央値・範囲・四分位範囲を算出する。t検定及びWilcoxon rank-sum testで比較する。さらに、0週からの変化量（12週時－0週時）についても同様のことを行う。なお、12週時は9～12週が目安になるが、その時点のデータがない場合には8週時（5～8週）のデータで代用する。

8.9　12 週時の貧血・血液状態に関する比較

貧血・血液状態については、12 週時の赤血球数、血色素量、ヘマトクリット値、血小板数で評価する。投与群と非投与群ごとに平均±標準偏差、及び、中央値・範囲・四分位範囲を算出する。t 検定及び Wilcoxon rank-sum test で比較する。さらに、0 週からの変化量（12 週時－0 週時）についても同様のことを行う。なお、12 週時は 9～12 週が目安になるが、その時点のデータがない場合には 8 週時（5～8 週）のデータで代用する。

8.10　12 週時の免疫状態に関する比較

免疫状態については、12 週時の CRP、白血球数、IgG, IgM, IgA, IgG サブクラスで評価する。投与群と非投与群ごとに、平均±標準偏差、及び、中央値・範囲・四分位範囲）を算出する。t 検定及び Wilcoxon rank-sum test で比較する。さらに、0 週からの変化量（12 週時－0 週時）についても同様のことを行う。なお、12 週時は 9～12 週が目安になるが、その時点のデータがない場合には 8 週時（5～8 週）のデータで代用する。

9.　安全性の解析

12 週中に発生した SAE(重篤な有害事象)については、投与群と非投与群ごとに人数と割合を算出する。2 群比較は、Pearson’s chi-square test 及び Fisher’s exact test で検定する。

副作用については、皮疹・じんま疹、むくみ、脱力・痙攣、倦怠感・黄疸、悪心・下痢を評価する[主治医経過録より引用]。それぞれの副作用別に、投与群と非投与群ごとに人数と割合を算出する。2 群比較は、Pearson’s chi-square test 及び Fisher’s exact test で検定する。

肝機能・腎機能については、AST(GOT), ALT(GPT), γ-GTP, LDH, T-Bil, クレアチニンを評価する[主治医経過録, p.18 より引用]。0 週(ベースライン)から 12 週にかけての変化量（12 週時－0 週時）に関して、投与群と非投与群ごとに平均±標準偏差を算出し、t 検定及び Wilcoxon rank-sum test で比較する。なお、12 週時は 9～12 週が目安になるが、その時点のデータがない場合には 8 週時（5～8 週）のデータで代用する。

電解質については、Na, Cl, K について評価する[主治医経過録, p.18 より引用]。0 週(ベースライン)から 12 週にかけての変化量(12 週時－0 週時)に関して、投与群と非投与群ごとに平均±標準偏差を算出し、t 検定及び Wilcoxon rank-sum test で比較する。なお、12 週時は 9～12 週が目安になるが、その時点のデータがない場合には 8 週時（5～8 週）のデータで代用する。

１０．　推移の解析

中耳炎については、開始前１ヵ月当たりの中耳炎の罹患回数、開始後１ヶ月目(1～4 週)の中耳炎の罹患回数、開始後２ヶ月目（5～8 週）の中耳炎の罹患回数、開始後３ヶ月目（9～12 週）の中耳炎の罹患回数の４時点について、平均値の推移を２群に分けて図示する(付録Ｂ)。

上気道炎については、開始後１ヶ月目(1～4 週)の上気道炎の罹患回数、開始後２ヶ月目（5～8 週）の上気道炎の罹患回数、開始後３ヶ月目（9～12 週）の上気道炎の罹患回数の３時点について、平均値の推移を２群に分けて図示する(付録Ｃ)。

抗菌薬の投与については、開始後１ヶ月目(1～4 週)の抗菌薬の投与日数、開始後２ヶ月目（5～8 週）の抗菌薬の投与日数、開始後３ヶ月目の抗菌薬の投与日数（9～12 週）の３時点について、の平均値の推移を２群に分けて図示する(付録Ｃ)。

中耳炎スコアについては、開始後１ヶ月目(1～4 週)の中耳炎スコア、開始後２ヶ月目（5～8 週）の中耳炎スコア、開始後３ヶ月目（9～12 週）の中耳炎スコアの３時点について、平均値の推移を２群に分けて図示する(付録Ｃ)。

患者日誌から算出した「発熱日数、耳痛、不機嫌、耳漏、膿性鼻漏、水様性鼻漏、咳」については、週ごとに有症日数を算出し、平均値の推移を２群に分けて図示する（付録Ｄ)。

１１．　サブグループ解析*

性別(男女別)、年齢区分別(1 歳未満，1 歳以上；2 歳未満，2 歳以上；1 歳未満，1～2 歳，2 歳以上)、体重区分別（7-10kg，10-15kg，15-20kg)、開始前の１ヵ月当たりの中耳炎の罹患回数の区分別(0-1 回、1-2 回、3 回以上)、通園状況別、哺乳状況別、家族の喫煙状況別、それぞれの「証」（活気、体温、汗、皮膚、顔色、嘔吐、下痢、食欲、咳）別に、一次エンドポイントと同様に（8.1 及び 8.2)、群間比較を実施する。

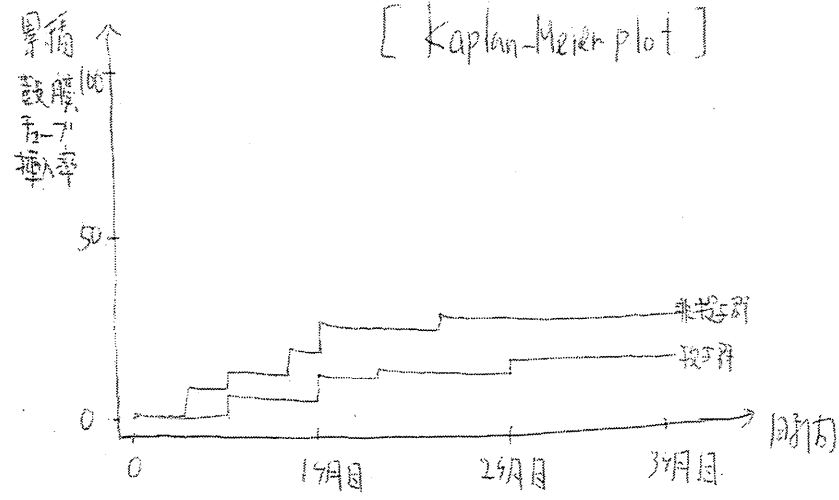
１２．　補足的解析*

まず投与群に限定し、有効例（定義 1．１ヵ月当たりの中耳炎の罹患回数が１回以上減少例；定義 2．１ヵ月当たりの中耳炎の罹患回数が 0.5 回以上減少例；定義 3．１ヵ月当たりの中耳炎の罹患回数が減少例）と無効例（有効例でない症例）について、それぞれの「証」（活気、体温、汗、皮膚、顔色、嘔吐、下痢、食欲、咳）との関連性を分析する。すなわち、虚証で有

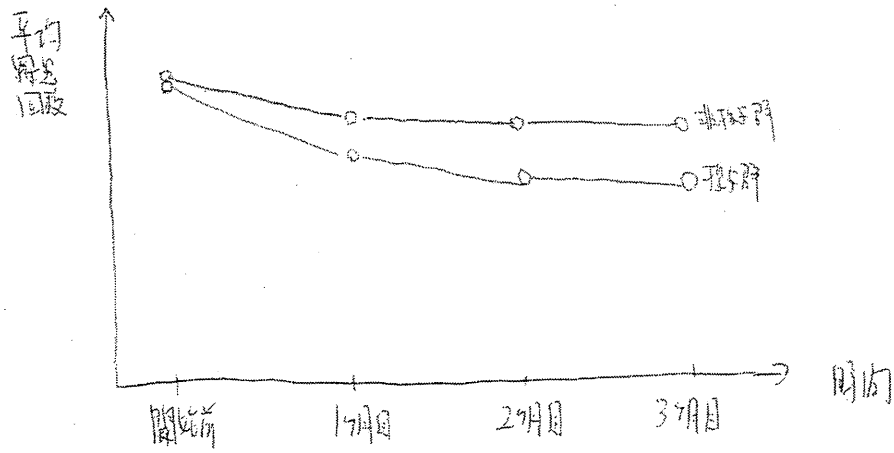
効例が多いか否かを検討する。その際、２×２クロス表にまとめ、Pearson’s chi-square test 及び Fisher’s exact test で検定する(付録E)。

同様に投与群に限定し、有効・無効と、年齢、性別、体重、開始前の１か月当たりの中耳炎の罹患回数、通園状況、哺乳状況、家族の喫煙との関連性を分析する。連続値（年齢、体重、投与前の１か月当たりの中耳炎の罹患回数）に関しては平均値の比較（t 検定及び Wilcoxon rank-sum test)、カテゴリー値（性別、通園状況、哺乳状況、家族の喫煙）に関してはクロス表と Pearson’s chi-square test により検定する。

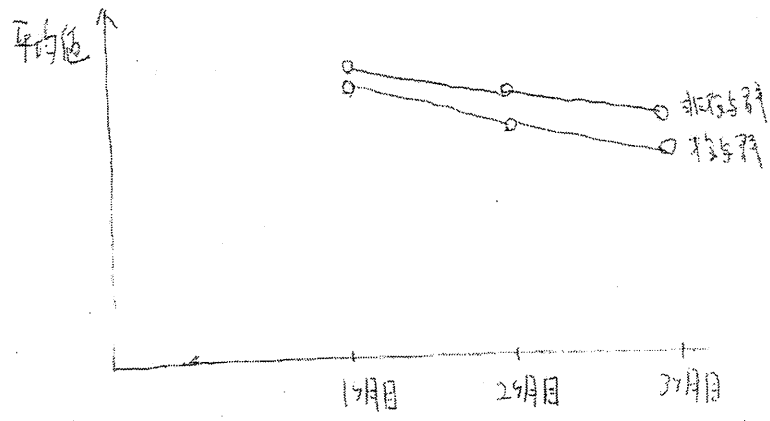
付録A


[Kaplan-Meier plot]
累積
設置
チューブ
挿入率
100
50
0
0
1カ月目
2カ月目
3カ月目
時間(日)

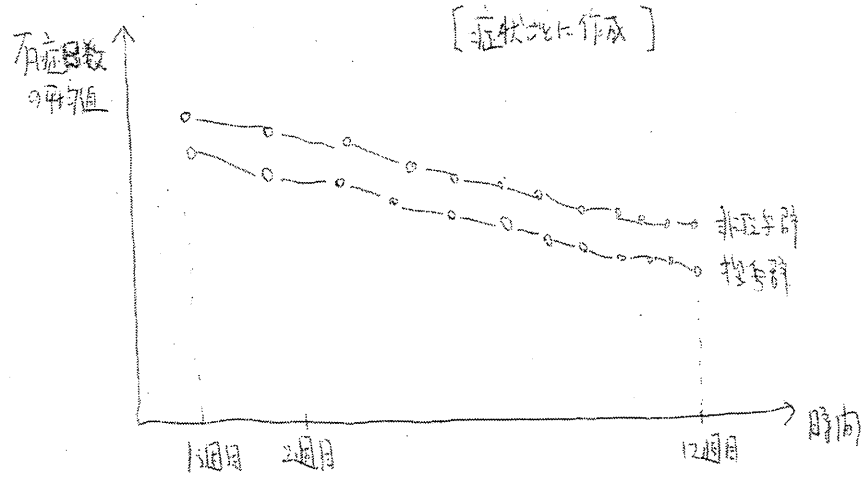
付録B


平均
開始
回数
時間
開始時
1カ月目
2カ月目
3カ月目

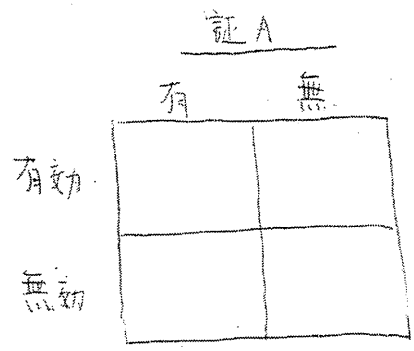
付録C


平均値
1カ月目
2カ月目
3カ月目

付録D



付録E



総括研究報告書

別添１

厚生労働科学研究費補助金

医療技術実用化総合研究事業

小児反復性中耳炎に対する十全大補湯の有用性に関する多施設共同二重盲検ランダム化比較試験(H21-臨床研究-一般-007)に関する研究

平成２３年度　総括研究報告書

研究代表者　吉崎　智一

平成２４（２０１２）年　５月