同意文書

私および代諾者は「小児反復性中耳炎に対する十全大補湯の治療効果に対する研究」の臨床試験に参加するにあたり，説明文書を受け取り，以下の内容について説明を受けました．本試験の内容（目的と方法など）を十分に理解しましたので，今回の試験に参加することについて私の自由意思にもとづいて同意いたします．説明文書と同意書を受け取りました。

- □ 臨床試験とは
- □ あなたの病気（症状）について
- □ 今回の臨床試験について
- □ 試験の方法について
- □ 予測される効果（効き目）と副作用について
- □ 健康被害が生じた場合の補償について
- □ 本試験終了後の治療について
- □ 試験参加に伴う費用負担について
- □ 記録の閲覧について
- □ あなたのプライバシー保護について
- □ 試験への参加の自由と同意撤回の自由について
- □ 他の治療法について
- □ 試験中止となる場合の条件又は理由
- □ あなたに守っていただきたいことについて
- □ この試験に係る資金ならびにスポンサーとの関わりについて
- □ 臨床試験に関する窓口

同意日：平成　　年　　月　　日

ご本人 氏名 ＿＿＿＿＿＿＿＿＿＿＿＿

〒　　－

現住所 ＿＿＿＿＿＿＿＿＿＿＿＿

代諾者　氏名 ＿＿＿＿＿＿＿＿＿＿＿＿

続柄（　　）

〒　　－

現住所（同上の場合省略可） ＿＿＿＿＿＿＿＿＿＿＿＿

説明日：平成　　年　　月　　日

所属 ＿＿＿＿＿＿＿＿＿＿＿＿

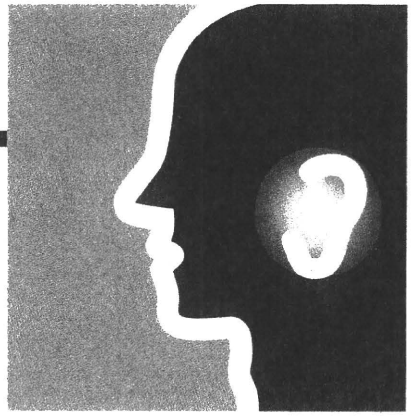
試験責任（分担）医師名 ＿＿＿＿＿＿＿＿＿＿＿＿

（医療施設保管用）

資料2

小児急性中耳炎診療ガイドライン

2009年版



編集
日本耳科学会
日本小児耳鼻咽喉科学会
日本耳鼻咽喉科感染症研究会

金原出版株式会社

案）は，ガイドライン作成委員のコンセンサスが得られた内容を付記として示した。

巻末に，治療アルゴリズムを呈示しているが，おのおのの治療アルゴリズムの3次治療においても軽快しない例は難治例とする。難治例の診療については，本ガイドラインでは対象としていない。

※付記　反復性中耳炎の診療についての提案

1）反復性中耳炎の定義

反復性中耳炎の定義は，国内外で標準化されたものはないが，本ガイドラインでは，比較的最近の論文で汎用されている過去6カ月以内に3回以上，12カ月以内に4回以上の急性中耳炎罹患と定義した（Sher et al. 2005, Ables et al. 2004, Arrieta et al. 2004）。

2）反復性中耳炎の病態とリスクファクター

反復性中耳炎の病態は，単純性の急性中耳炎を繰り返すタイプと，滲出性中耳炎に罹患している患耳が急性増悪として単純性の急性中耳炎を繰り返すタイプに分類される。

反復性中耳炎のリスクファクターとしては，低年齢，起炎菌の耐性化，罹患者の免疫能，生活・環境要因が提唱されている。2歳未満の低年齢は遺伝学的背景からもリスク因子となると報告されている（Wiertsema et al. 2006）。起炎菌では，多剤耐性の肺炎球菌が原因であることが多いという報告（van Kempen et al. 2004）もあり，抗菌薬の効果の低下に伴い，鼻咽腔からの不十分な除菌が反復化の一つの要因と考えられている。宿主の起炎菌に対する低い免疫応答の関与も重要である（Yamanaka et al. 2008）。母乳として母体から得られる免疫能と反復性中耳炎の発症の関連も推測され，母乳哺育の欠如が反復性中耳炎発症の高いリスクとされている（Lubianca Neto et al. 2006）。生活・環境に関する要因としては，兄弟あり，保育園児，おしゃぶりなどがリスクファクターとなっている（Lubianca Neto et al. 2006）。

3）反復性中耳炎の治療

前述した要因が，反復性中耳炎発症のリスクファクターと想定され，起炎菌の耐性化に対しては，抗菌薬投与の前に必ず細菌の感受性検査を行い，適切な投与量の抗菌薬の選択が必要となる。推奨される抗菌薬は本ガイドラインで提示した。

肺炎球菌ワクチン接種が，欧米では反復性中耳炎の予防目的として用いられている。オランダからは，7価蛋白結合型肺炎球菌ワクチンと肺炎球菌多糖体ワクチン接種の二重盲検ランダム化比較試験で，反復性中耳炎の罹患頻度の有意な減少はなかったと報告されている（Brouwer et al. 2005）。また，Cochrane Reviewでは肺炎球菌多糖体ワクチンの有用性は認めるも，蛋白結合型ワクチンは推奨されていない（Straetemans et al. 2004）。一方，チェコからの二重盲検ランダム化比較試験では，インフルエンザ菌D蛋白結合11価莢膜肺炎球菌多糖体ワクチンが，肺炎球菌ならびにインフルエンザ菌による急性中耳炎に有意な予防効果が認められている（Prymula et al. 2006）。わが国では，2009年には7価蛋白結合型肺炎球菌ワクチンが認可される予定である。このワクチンは，本邦の小児急性中耳炎中耳貯留液より分離された肺炎球菌の血清型の62.9%，薬剤耐性菌の78.0%をカバーしており，肺炎球菌に対しては34.4～62.5%，薬剤耐性肺炎球菌に対しては39.8～49.1%の予防効果が期待されている。また，交叉反応性も含めると急性中耳炎全体として，7.6～9.4%の予防効果が期待される。

わが国独自の治療として提唱されているのが，漢方補剤による免疫能の上昇由来による予防効果で，十全大補湯の有効性が報告された（Maruyamaら2008）。

外科的治療として，アデノイド切除術はランダム化比較試験で，反復性中耳炎の頻度を減少させることはなく，予防効果もないとされている（Oomen et al. 2005, Hammaren-Malmi et al. 2005, Koivunen et al. 2004）。一方，鼓膜切開術は本邦の症例対照研究で，反復性中耳炎の発症頻度低下に有意な効果は認められていないが（Nomura et al. 2005），鼓膜換気チューブの1年あるいは1カ月の短期留置で罹患頻度の有意な低下が示されている（宇野 2007a, b）。生活・環境の要因に対処するには，集団保育の中止と，母乳哺育が望ましい。

1) Sher L, Arguedas A, Husseman M, Pichichero M, Hamed KA, Biswas D, Pierce P, Echols R. Randomized, investigator-blinded, multicenter, comparative study of gatifloxacin versus amoxicillin/clavulanate in recurrent otitis media and acute otitis media treatment failure in children. Pediatr Infect Dis J. 2005；24(4)：301-8.
2) Ables AZ, Warren PK. High-dose azithromycin or amoxicillin-clavulanate for recurrent otitis media? J Fam Pract. 2004；53：186-8.
3) Arrieta A, Singh J. Management of recurrent and persistent acute otitis media：new options with familiar antibiotics. Pediatr Infect Dis J. 2004；23：S115-24.
4) Wiertsema SP, Herpers BL, Veenhoven RH, Salimans MM, Ruven HJ, Sanders EA, Rijkers GT. Functional polymorphisms in the mannan-binding lectin 2 gene：effect on MBL levels and otitis media. J Allergy Clin Immunol. 2006；117：1344-50.
5) van Kempen MJ, Vaneechoutte M, Claeys G, Verschraegen GL, Vermeiren J, Dhooge IJ. Antibiotic susceptibility of acute otitis media pathogens in otitis-prone Belgian children. Eur. J Pediatr. 2004；163：524-9.
6) Yamanaka N, Hotomi M, Billal DS. Clinical bacteriology and immunology in acute otitis media in children. J Infect Chemother. 2008；14(3)：180-7.
7) Lubianca Neto JF, Hemb L,Silva DB. Systematic literature review of modifiable risk factors for recurrent acute otitis media in childhood. J Pediatr (Rio J). 2006；82：87-96.
8) Brouwer CN, Maille, AR, Rovers MM, Veenhoven RH, Grobbee DE, Sanders EA, Schilder AG. Effect of pneumococcal vaccination on quality of life in children with recurrent acute otitis media：a randomized, controlled trial. Pediatrics. 2005；115：273-9.
9) Straetemans M, Sanders EAM, Veenhoven RH, Schilder AGM, Damoiseaux RAMJ, Zielhuis GA. Pneumococcal vaccines for preventing otitis media. Cochrane Database of Systematic Reviews. 2004 issue 1.
10) Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, Kohl I, Lommel P, Poolman J, Prieels JP, Schuerman L. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae：a randomised double-blind efficacy study. Lancet. 2006；367：740-8.
11) Maruyama Y, Hoshida S, Furukawa M, Ito M. Effects of Japanese herval medicine, Juzen-taiho-to, in otitis-prone children -a preliminary study. Acta Otolaryngol 2008 Jun 12：1-5 (Epub ahead of print).
12) Oomen KP, Rovers MM, van den Akker EH, van Staaij BK, Hoes AW, Schilder AG. Effect of adenotonsillectomy on middle ear status in children. Laryngoscope. 2005；115：731-4.
13) Hammaren-Malmi S, Saxen H, Tarkkanen J, Mattila PS. Adenoidectomy does not significantly reduce the incidence of otitis media in conjunction with the insertion of tympanostomy tubes in children who are younger than 4 years：a randomized trial. Pediatrics. 2005；116(1)：185-9.
14) Koivunen P, Uhari M, Luotonen J, Kristo A, Raski R, Pokka T, Alho OP. Adenoidectomy versus chemoprophylaxis and placebo for recurrent acute otitis media in children aged under 2 years：randomised controlled trial. BMJ (Clinical research ed.). 2004；328：487.
15) Nomura Y, Ishibashi T, Yano J, Ichikawa T, Shinogami M, Monobe H, Hirai R, Kaga K. Effect of myringotomy on prognosis in pediatric acute otitis media. Int J Pediatr Otorhinolaryngol. 2005；69：61-4.
16) 宇野芳史：小児難治性反復性中耳炎に対する長期鼓膜換気チューブ留置術の有効性について．Otol Jpn. 2007(a)；17：16-25.

17) 宇野芳史：小児難治性反復性中耳炎に対する短期鼓膜換気チューブ留置術の有効性について．Otol Jpn .2007(b)：17：194-202.

8. 急性中耳炎の定義

本診療ガイドラインでは，急性中耳炎を，「急性に発症した中耳の感染症で，耳痛，発熱，耳漏を伴うことがある」と定義した。さらに以下の注釈を加えた。

注　釈

①急性に発症とは，本人の訴えあるいは両親や保護者により急性症状が発見され，その48時間以内に受診した場合と定義する(Harabuchi et al. 2001)。急性炎症の持続期間については，明確なエビデンスは存在しないが，3週を超えないとする定義が一般的であるので本ガイドラインでも採用する。また慢性中耳炎の急性増悪は急性中耳炎とは病態が異なるので除く。

②米国小児科学会が報告した急性中耳炎ガイドライン(Subcommittee on Management of Acute Otitis Media 2004)では，急性中耳炎と診断するには下記のような症状，徴候が求められるとしている。

(1) 中耳の炎症と貯留液による症状，徴候が最近，通常突然に発症

(2) 鼓膜の膨隆，可動性の喪失・制限，貯留液の透見，耳漏により中耳貯留液の存在

(3) 鼓膜の発赤，耳痛がみられて明らかな中耳炎の徴候と症状の存在

9. 本邦における小児急性中耳炎症例からの検出菌と抗菌活性

(1) 小児急性中耳炎からの検出菌について

2007年の第4回耳鼻咽喉科領域感染症臨床分離菌全国サーベイランス(2007年1月～6月に施行)結果報告(鈴木ら 2008)では，過去4回(1994年，1998年，2003年，2007年)施行した全年齢における急性中耳炎からの検出菌頻度年次推移が報告された(**図1**，**表2**)。肺炎球菌の検出頻度は増加傾向にあり，2007年のサーベイランスでは34.1％を占め，インフルエンザ菌は2003年のサーベイランスまでは増加傾向にあったが，2007年はやや減少に転じ24.2％であった。黄色ブドウ球菌は減少し4.4％であった。モラキセラ・カタラーリス菌は2003年は7.1％，2007年は4.4％検出された。15歳未満の小児急性中耳炎の非鼓膜穿孔症例の中耳貯留膿汁45検体からは，インフルエンザ菌22.2％，肺炎球菌が46.7％検出され，モラキセラ・カタラーリスが4.4％検出された。鼓膜が自潰穿孔した中耳流出膿汁23検体からは，黄色ブドウ球菌の検出率が8.7％に増加し，インフルエンザ菌が47.8％，肺炎球菌が8.7％を占めた(**表3**)。急性中耳炎の起炎菌として，インフルエンザ菌，肺炎球菌，モラキセラ・カタラーリス，化膿連鎖球菌は重要であると考えられるが，黄色ブドウ球菌は主として経外耳道的混入菌と考えられ，起炎菌としては考えにくい。インフルエンザ菌，肺炎球菌，モラキセラ・カタラーリスが3大起炎菌であるのは，欧米の報告でも同様で，Turner らは，生後2カ月以内の109例122件の検出菌の内訳を，インフルエンザ菌34％，肺炎球菌46％，モラキセラ・カタラーリス2％と報告している。Commissoら(2000)のアルゼンチンの報告でも，肺炎球菌が39.4％，インフルエンザ菌が32.7％と大多数を占めている。

2007年の耳鼻咽喉科領域感染症臨床分離菌全国サーベイランスで成人を含めた全症例の内訳は，94例(急性化膿性中耳炎)，95例(急性副鼻腔炎)，91例(急性扁桃炎)，69例(扁桃周囲膿瘍)，95例(慢性中耳炎)，90例(慢性副鼻腔炎)である。この症例から得られた63株のインフルエンザ菌中，26株

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

[1]Family Health International, Research Triangle Park, NC 27709, USA
[2]Centre for Statistics in Medicine, University of Oxford, Wolfson College, Oxford
[3]Ottawa Methods Centre, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada
Correspondence to: K F Schulz
kschulz@fhi.org

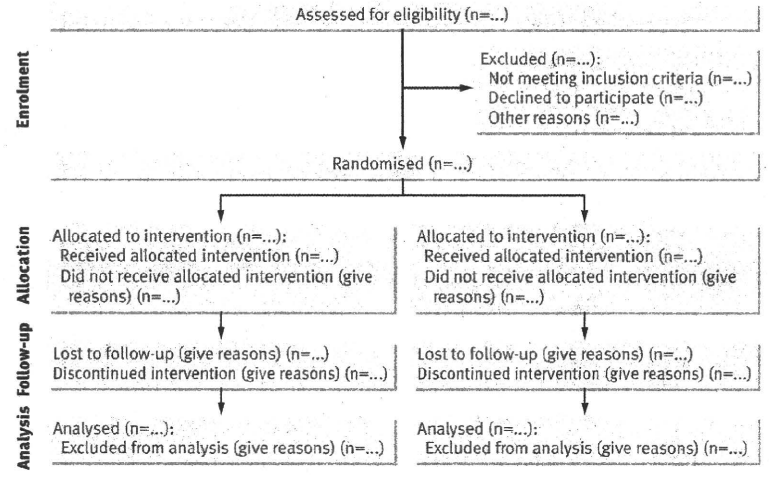
Accepted: 9 December 2009

Cite this as: *BMJ* 2010;340:c332
doi: 10.1136/bmj.c332

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.

The CONSORT Group contributors to CONSORT 2010: DG Altman, Centre for Statistics in Medicine, University of Oxford; Virginia Barbour, *PLoS Medicine*; Jesse A Berlin, Johnson & Johnson Pharmaceutical Research and Development, USA; Isabelle Boutron, University Paris 7 Denis Diderot, Assistance Publique des Hôpitaux de Paris, INSERM, France; PJ Devereaux, McMaster University, Canada; Kay Dickersin, Johns Hopkins Bloomberg School of Public Health, USA; Diana Elbourne, London School of Hygiene & Tropical Medicine; Susan Ellenberg, University of Pennsylvania School of Medicine, USA; Val Gebski, University of Sydney, Australia; Steven Goodman, *Journal of the Society for Clinical Trials*, USA; Peter C Gøtzsche, Nordic Cochrane Centre, Denmark; Trish Groves, *BMJ*; Steven Grunberg, American Society of Clinical Oncology, USA; Brian Haynes, McMaster University, Canada; Sally Hopewell, Centre for Statistics in Medicine, University of Oxford; Astrid James, *Lancet*; Peter Juhn, Johnson & Johnson, USA; Philippa Middleton, University of Adelaide, Australia; Don Minckler, University of California Irvine, USA; D Moher, Ottawa Methods Centre, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Canada; Victor M Montori, Knowledge and Encounter Research Unit, Mayo Clinic College of Medicine, USA; Cynthia Mulrow, *Annals of Internal Medicine*, USA; Stuart Pocock, London School of Hygiene & Tropical Medicine; Drummond Rennie, *JAMA*, USA; David L Schriger, *Annals of Emergency Medicine*, USA; KF Schulz, Family Health International, USA; Iveta Simera, EQUATOR Network; Elizabeth Wager, Sideview.

Contributors to CONSORT 2010 who did not attend the Montebello meeting: Mike Clarke, UK Cochrane Centre; Gordon Guyatt, McMaster University, Canada.

Funding: We received financial support from United Kingdom National Institute for Health Research and the Medical Research Council; Canadian Institutes of Health Research; Presidents Fund, Canadian Institutes of Health Research; Johnson & Johnson; *BMJ*; and the American Society for Clinical Oncology. DGA is supported by Cancer Research UK. DM by a University of Ottawa Research Chair, and KFS by Family Health International. None of the sponsors had any involvement in the planning, execution, or writing of the CONSORT documents. Additionally, no funder played a role in drafting the manuscript.

Competing interests: Uniform disclosure of potential conflicts of interest: all authors have completed the ICMJE unified competing interest form at www.icmje.org/coi_disclosure.pdf (available from the corresponding author) and declare (1) DM received grants for this work from Johnson & Johnson, *BMJ*, and American Society for Clinical Oncology; KFS and DGA received support for travel to meetings for this work from Johnson & Johnson, *BMJ*, and American Society for Clinical Oncology; (2) KFS and DA had travel expenses reimbursed by the EQUATOR Network; KFS has received honoraria for delivering educational presentations for the American Board of Obstetrics and Gynecology Foundation for Excellence in Women's Health Care, Ortho-McNeil Janssen Scientific Affairs, and the American College of Obstetrics and Gynecology; and has done consultancy for Wyeth. All authors also declare (3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) no non-financial interests that may be relevant to the submitted work.

1 Jüni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001;323:42-6.
2 Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet* 2005;365:1159-62.
3 Glasziou P, Meats E, Heneghan C, Shepperd S. What is missing from descriptions of treatment in trials and reviews? *BMJ* 2008;336:1472-4.
4 Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS ONE* 2008;3:e3081.
5 Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;276:637-9.
6 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191-4.
7 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Ann Intern Med* 2001;134:657-62.
8 Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;285:1987-91.
9 Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill C, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *Med J Aust* 2006;185:263-7.
10 Hopewell S, Dutton S, Yu L-M, Chan A-W, Altman DG. The quality of reports of randomised trials in 2000 and 2006: a comparative study of articles indexed by PubMed. *BMJ* 2010;340:c723.
11 Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *BMJ* 2004;328:702-8.
12 Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;295:1152-60.
13 Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c869.
14 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.
15 Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352:609-13.
16 Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
17 Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;326:41-4.
18 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, for the STROBE Initiative. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806-8.
19 Standards of Reporting Trials Group. A proposal for structured reporting of randomized controlled trials. *JAMA* 1994;272:1926-31.
20 Rennie D. Reporting randomized controlled trials. An experiment and a call for responses from readers. *JAMA* 1995;273:1054-5.
21 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008;371:281-3.
22 Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;291:2457-65.
23 Sackett DL. Commentary: Measuring the success of blinding in RCTs: don't, must, can't or needn't? *Int J Epidemiol* 2007;36:664-5.
24 Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet* 2002;359:696-700.
25 Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, Briel M, et al. Randomized trials stopped early for benefit: a systematic review. *JAMA* 2005;294:2203-9.
26 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;319:670-4.
27 Nuovo J, Melnikow J, Chang D. Reporting number needed to treat and absolute risk reduction in randomized controlled trials. *JAMA* 2002;287:2813-4.
28 Ioannidis JP, Evans SJ, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004;141:781-8.
29 De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *Lancet* 2004;364:911-2.
30 Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167-70.
31 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 2008;5:e20.
32 Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008;148:295-309.
33 Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. *Ann Intern Med* 2006;144:364-7.
34 Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008;337:a2390.

資料4

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

富山大学大学院医学薬学研究部
バイオ統計学・臨床疫学
教授　折笠秀樹

Version 0.1 (2010/11/04)
Version 0.2 (2010/12/13)
Version 0.3 (2010/12/21)

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。

なお、本臨床試験は厚生労働省科学研究費補助金（H21-臨床研究--一般-007）において施行される。

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の急性中耳炎(AOM)のを十全大補湯による急性中耳炎（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 を用いる。

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

３．３　目標症例数

全体で 100 症例

３．４　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.) を参照する。

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、JMP 8.0 及び SPSS VersionXXX を用いる。

５．　解析対象集団

CONSORT2010 声明に基づき、登録症例の経過中の被験者のフローチャートを作成する。すなわち、登録患者数、ランダム割り付け前に除外された症例数及びその内訳、ランダム割り付けされた症例数（投与群、非投与群別に)、ランダム割り付けから 12 週終了までの間に生じた中止・脱落症例数（投与群、非投与群別に）及びその内訳、12 週完遂した症例数（投与群、非投与群別に)、及びそれぞれの割合を算出する。

主な解析対象集団は、ランダム割り付けされた症例数とする（ＩＴＴ(Intention-to-treat)解析対象集団と称する)。また、12 週完遂した症例数に基づく解析も実施する（ＰＣ(Protocol compatible)解析集団と称する)。

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)
・開始前の１ヶ月当たりに換算したAOM平均罹患回数（平均±標準偏差、及び中央値・範囲・四分位範囲)
・家族の喫煙Tobacco smoke exposure（有無別の人数と割合）
・通園状況（有無別の人数と割合）
・哺乳状況（有無別の人数と割合）
・抗生物質（有無別の人数と割合）

８．　有効性の解析

一次エンドポイント：

急性中耳炎の罹患回数(12週中)

12 週間の観察期間中の急性中耳炎(AOM)の罹患回数 Number of AOM episodes に関して、まず１ヶ月当たりに換算した平均罹患回数を被験者ごとに算出する。こ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。

開始前のAOM平均罹患回数（１ヶ月当たりに換算した）と、開始後12週中のAOM平均罹患回数（１ヶ月当たりに換算した）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。

急性中耳炎の初回再発までの日数に関して、Kaplan-Meier plot 及び Log-rank test を実施する。必要データとしては、被験者ごとに急性中耳炎再発の有無、無の場合は何日目まで無か、有の場合は初回再発までの日数である。横軸に12週までの時間軸を取り、縦軸は累積での再発率となる(付録Ａ参照)。

二次エンドポイント：

・上気道炎の罹患回数（12週中）
・中耳炎スコア（12週時）
・発熱・耳痛・臨床症状（12週中）

・栄養状態（12 週時）
・貧血・血液状態（12 週時）
・免疫状態（12 週時）
・抗生物質の投与(12 週中)
・鼓膜チューブ挿入(12 週中)

12 週中の上気道炎の罹患回数は１ヵ月当たりの罹患回数に換算し、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。１ヵ月当たりの上気道炎の罹患回数に関しては、t 検定及び Wilcoxon rank-sum test で比較する。

中耳炎スコアについては、12 週時のスコアに関して、投与群と非投与群ごとに平均±標準偏差、及び、中央値・範囲・四分位範囲を算出する。また、12 週時の平均スコアの違いについては、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。

発熱、耳痛、不機嫌、耳漏、膿性鼻漏、水様性鼻漏、せきについては、12 週中の有症週の割合（これを有症割合と称す；12 週中の 6 週で症状が有なら 50%）を被験者ごとに算出し、投与群と非投与群ごとに有症割合の平均±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。

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。

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。

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。

抗生物質の投与については、12 週中の抗生物質の投与日数で評価する。その日数を１カ月当たりの日数に換算した値（１ヵ月当たりの抗生物質の投与日数）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）を算出する。t 検定及び Wilcoxon rank-sum test で比較する。

12 週中の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。2 群比較は、Pearson’s chi-square test 及び Fisher’s exact test で検定する。

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。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。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。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

AOM罹患回数については、開始前１ヵ月当たり換算値、開始後１ヶ月目(1～4週)の回数、開始後2ヶ月目（5～8週）の回数、開始後3ヶ月目の回数（9～12週）の4時点について、AOM罹患回数の平均値の推移を2群に分けて図示する(付録Ｂ)。

上気道炎の罹患回数については、開始後１ヶ月目(1～4 週)の回数、開始後2ヶ月目（5～8週）の回数、開始後3ヶ月目の回数（9～12週）の3時点について、上気道炎罹患回数の平均値の推移を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)のスコア、開始後 2ヶ月目（5～8週）のスコア、開始後3ヶ月目のスコア（9～12週）の3時点について、中耳炎スコアの平均値の推移を2群に分けて図示する(付録Ｃ)。

発熱、耳痛、不機嫌、耳漏、膿性鼻漏、水様性鼻漏、せきについては、1週ごとに有症割合を算出し、各症状の有症割合の推移を 2 群に分けて図示する（付録Ｄ）

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

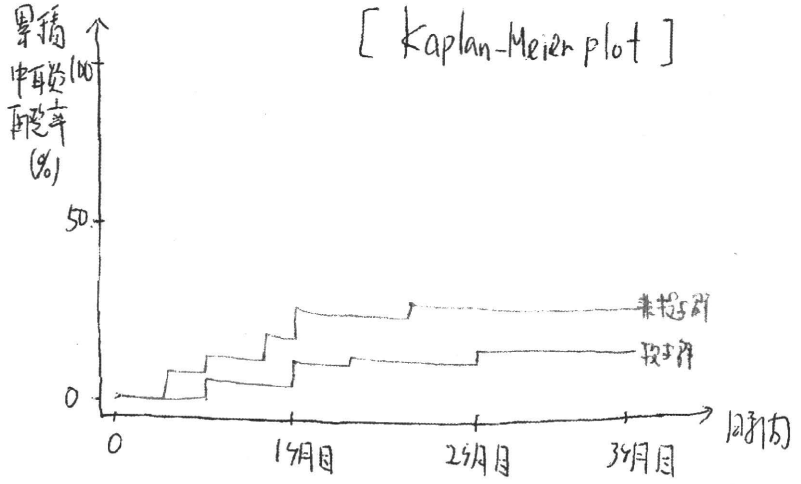
１１．　サブグループ解析

性別(男女別)、年齢区分別(１歳未満、１歳以上)、体重区分別（7-10kg, 10-15kg, 15-20kg)、投与前の１ヵ月当たりAOM罹患回数の区分別(0-1 回、1-2 回、3 回以上)、「証」（汗をかきやすいか、色白か、など）別に、一次エンドポイントと同様の解析を実施する。

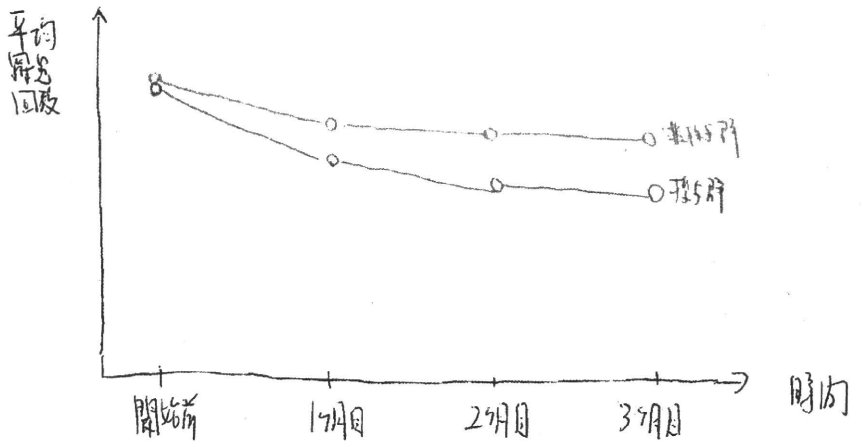
１２．　補足的解析

投与群の中での有効例（１ヵ月当たり AOM 罹患回数の１回以上減少例）と無効例（有効例でない症例）について、それぞれの「証」との関連性を分析する。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)。

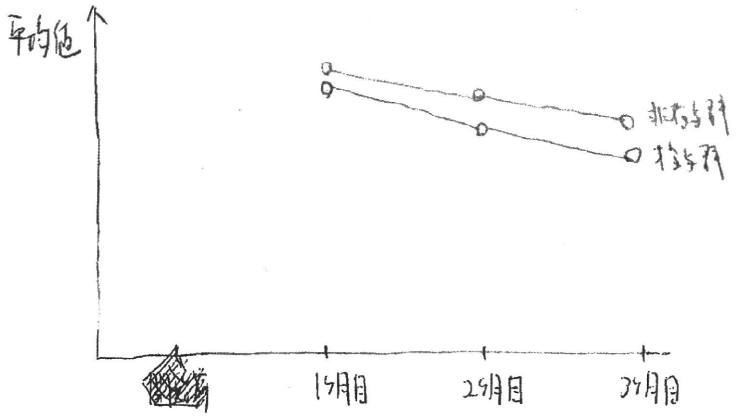
付録A


[Kaplan-Meier plot]
累積
中耳炎
再発率
(%)
100
50
0
0
1カ月目
2カ月目
3カ月目
時間

付録B


平均
膿汁
回数
時間
開始前
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