“Sorting out Lemons and Oranges:”
Towards Better Quality of Reporting Clinical Trials in

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INTRODUCTION

The editorial in this first issue of Journal of Physical Therapy welcomes its readers with a historical note of clinical trials and in Physical Therapy and the need for a change as a part of paradigm shift in research, not only in the conduct of clinical trials but also in their reporting, as recommended by CONsolidated Standards Of Reporting Trials (CONSORT) statement- 2010.

History of clinical trial:

According to The Old Testament, King Nebuchadnezzar ruled Babylon for almost 60 years, his reign ending in 562 BC. During his reign, according to the “Book of Daniel” in The Bible, Nebuchadnezzar ordered his people to eat only meat and drink only wine, a diet he believed would keep them in perpetual health. Herbivorous youth who refused were ordered to eat only legumes and drink water. The comparison lasted 10 days after which he again ordered assessment of their health.

When Nebuchadnezzar’s experiment ended, the bean-loving men appeared better nourished than the mandated meat-eaters, the king then allowed them to continue their diet.¹

Clinical trials often involve studies performed on patients on effectiveness of interventions and/or their comparisons. Historically, the first “published” clinical trial was performed in 1747, on board the ship- Salisbury by then Scottish Physician, Dr James Lind (1716-1794),

ABSTRACT

The editorial aims to welcome the JPT readers to its first issue on a historical note of clinical trials in the field of Medicine and the Consolidated Standards Of Reporting Trials (CONSORT) statement’s reporting guidelines. History of research and randomized controlled trials (RCTs) in physiotherapy and the continuous growth in number of RCTs in physiotherapy evidence database (PEDro) necessitates better quality in reporting clinical trials by use of CONSORT checklist and flow diagram for clinical trials. Recently, the CONSORT statement was revised in 2010 and JPT became a journal endorser of the statement in its new version. The last section of the editorial envisions the aims of Journal of Physical Therapy in improving quality of reporting trials published by mandating the use of the statement.

Key words: clinical trial reporting, CONSORT 2010 statement, guidelines for reporting, randomized controlled trials.

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¹ Key points and pre-publication history of this article is available at the end of the paper.
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which he performed on his
shipmen with Scurvy. In his own
book, A Treatise on the
Scurvy,² (figure-1) he described
as follows, his first ever clinical
experiment on the ship (figure-2).

Figure-1. Coverpage of the
book, “A Treatise on the
Scurvy” by Dr James Lind.

“……Of the Prevention of the
Scurvy
I shall conclude the precepts
relating to the preservation of
seamen with showing the best
means of obviating many
inconveniences which attend
long voyages and of removing
the several causes productive
of this mischief. The following
are the experiments...

…..On the 20th May 1747, I took
twelve patients in the scurvy, on
board the Salisbury at sea.
Their cases were as similar I
could have them. They all in
general had putrid gums, the
spots and lassitude, with
weakness of their knees. They
lay together in one place, being

Figure-2. An artist’s work of depiction of the historical
clinical trial by Dr James Lind.

a proper apartment for the
sick in the fore-hold; and had
one diet common to all, viz.,
water-gruel sweetened with
sugar in the morning; fresh
mutton broth often times for
dinner; at other times
puddings, boiled biscuit with
sugar etc. And for supper,
barley and raisins, rice and
currants, sago and wine, or
the like. Two of these were
ordered each a quart of cider
a day, upon an empty
stomach; using a gargle
strongly acidulated with it for
their mouths. Two others took
two spoonfuls of vinegar three
times a day, upon an empty
stomach: having their gruels
and their food well acidulated
with it, as also the gargle for
their mouths. Two of the
worst patients, with the
tendons in the hamrigid (a
symptom none of the rest
had) were put under a course
sea-water. Of this they drank
half a pint every day, and
sometimes more or less as it
operated, by way of a gentle
physic. Two others had each
two oranges and one lemon
given them every day. These
they eat with greediness, at
different times, upon an
empty stomach. They
continued but six days under
this course, having consumed
the quantity that could be
spared. The two remaining
patients, took the bigness of a
nutmeg three times a day of
an electuate recommended
by a hospital-surgeon, made
of garlic, mustard-feed, rad.
Raphan, balsam of Peru, and
gum myrr; using for common
drink barley water well
acidulated with tamarinds; by
a decoction of which, with the
addition of cremor tartar, they
were greatly purged three or
four times during the course.
The consequence was, that
the most sudden and visible
good effects were perceived
from the use of the oranges
and lemons; one of those who
had taken them, being at the
end of six days fit for duty.
The spots were not indeed at
that time quite off his body,
nor his gums sound; but
without any other medicine,
than a gargle of vitriol, he
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became quite healthy before we came into Plymouth, which was on the 16th June. The other was the best recovered of any in his condition; and being now deemed pretty well, was appointed nurse to the rest of the sick."

The above “story” clearly depicted the importance of use of oranges and lemons for treating scurvy. The following six important queries arise on reading the above information:

How many Scurvy patients participated in “his” study?
How many treatment groups were there in “his” study?
What treatments were given for each of the groups?
How many patients were there in each of the treatment groups?
How many of “his” patients completed the study?
How can we conclude “oranges and lemons” are the only effective remedy for Scurvy?

I hope our JPT readers would be able to answer these at the end of reading this paper. Historically however, Medical scientists were very skeptical in “his” findings. There was a growing controversy in the interpretation of “his” findings into either as rationally-derived experimentation or controlled empiricism. It took nearly forty-two years for the relevant authorities and The Navy Sick and Hurt Board to address the issue based on Dr. Lind’s study results. It should be recalled, however, that even Lind probably did not think of scurvy as primarily a nutritional disorder and the theory that antiscorbutics functioned by replacing a missing dietary component did not emerge until formulated by George Budd (1808-1882) over half a century later.5

It took two centuries afterwards to implement this into routine clinical practice. It took less than a century for the scientists to find out that vitamin C was involved in the disease and another to find out that oranges and lemons had in them, greater content of vitamin C. It was finally in 1930s, that it was found the anti-scorbutic factor was Vitamin-C.3

<table>
<thead>
<tr>
<th>Table-1: Types of clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose of clinical trial</strong></td>
</tr>
<tr>
<td>Treatment</td>
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<tr>
<td>Prevention</td>
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<tr>
<td>Diagnostic</td>
</tr>
<tr>
<td>Screening</td>
</tr>
<tr>
<td>Quality of life</td>
</tr>
</tbody>
</table>

Source: U.S National Institutes of Health

<table>
<thead>
<tr>
<th>Table-2: Phases of clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase of clinical trial</strong></td>
</tr>
<tr>
<td>Phase-I</td>
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<td>Phase-II</td>
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<td>Phase-III</td>
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<tr>
<td>Phase-IV</td>
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</tbody>
</table>

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What is a clinical trial?

Meinert and Tonascia in their text Clinical Trials: Design, Conduct, and Analysis explain the term “clinical trials” as follows:

“Trial is from the Anglo-French trier, meaning to try. Broadly, it refers to the action or process of putting something to a test or proof. Clinical is from clinic, from the French clinique and from the Greek klinike, and refers to the practice of caring for the sick at the bedside. Hence, narrowly, a clinical trial is the action or process of putting something to a test or proof at the bedside of the sick.”

Clinical trials are classified into five categories depending upon their purpose: treatment, prevention, diagnostic, screening and quality of life. The interventional studies or treatment trials can further be divided into four phases (table-2) for conduct of the study at various levels to answer a research question valid enough to imply for a target population.

The objective of a clinical trial is to study the effects of a relatively less scientifically established intervention. The intervention to be studied is the experimental intervention and the patients in the group are termed as experimental group. The comparison group may be another intervention or a group either without any intervention (control), or a deceivably similar but no-effect intervention (sham) or a psycho-motivating intervention (placebo). Randomized controlled trials are for studying comparison between a control group and one or more experimental groups while randomized clinical trials are for comparison between two or more experimental groups. However, many authors use these terms interchangeably thus misleading the reading clinical community. This is explainable by the known fact that studying a group truly without administering any treatment for its effects, is deemed to be unethical in a clinical situation where the patient-centered treatment-decisions and payer’s policies influence on bio-ethical grounds.

Lind’s experiment in 1747 was a “controlled” clinical trial; the first use of sham procedure for comparison was done by Haygarth in 1799 and of placebo treatment as a comparison group was done by Gull in 1863. Historically, sham procedure was used much earlier than placebo treatments in randomized trials.

Sham-controlled trials are often used in studying treatment techniques which involve non-physiological effects like Manual Physical Therapy where it is widely believed that hands-on touch of the therapist will eventually lead to subjective relief of symptoms more than actual biomechanical effects of the technique. Placebo-controlled trials are often used in studying interventions with probable psychological/perceptual effects. For example, comparing ultrasound with laser therapy is a randomized clinical trial; comparing ultrasound with no treatment is a randomized controlled trial; comparing ultrasound with detuned (switched-off) ultrasound is a sham-controlled trial; and, comparing ultrasound with verbally positively-reinforced supine-lying is a placebo-controlled trial.

Clinical trials are done on patients and hence clinical decision-making was supposed to be “informed” rather than being “driven” by evidence from such trial’s findings. Randomized controlled/ clinical trials (RCTs) are the single-most individual level of evidence for evidence-based practice (EBP) in applying study results for interventions. The rigorous methodology adopted in RCTs is sometimes argued to be impractical and does not mimic real-life clinical practice situations. The term “randomized” in RCT implies either random sampling of patients for recruitment into the study or random allocation of patients to receive either of the interventions studied.

History of Clinical trials in Physical Therapy:

Journals are acknowledged as crucial sources of evidence-based information relevant to physiotherapy practice. The first research about physical therapy in the United States was published in March 1921 in The PT Review.
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On a historical note, the first ever randomized controlled trial in Physical Therapy evaluated Ultra-Violet radiation therapy and was published in 1929 by Dora Colebrook (figure-3) in Medical Research Council Special Report Series. Initially the RCTs were published in medical journals and not until 1967, for the first time an RCT evaluating physical therapy intervention was published in a physical therapy journal. This unique credit goes to author-Landen B whose study evaluated superficial heat vs. cold in LBP and was published in Physical Therapy journal.

Presently as was on March 2010, there were 15,920 records in Physiotherapy Evidence Database (PEDro) which includes 13,096 randomized controlled trials in physiotherapy alone. In April 2010, there are 13,189 RCTs (Figure-4). The last month thus witnessed an increase of 93 RCTs in a month- an average of 3 RCTs added to PEDro every day. This is the number for trials added to PEDro database alone. This number is the best example of “tip of an iceberg”

The actual number of trials in Physical Therapy will be a lot different considering

Figure-3. Cover page of the first RCT in physical therapy in Medical Research Council Special Report Series in 1929.

Figure-4: Showing the steady increase in the number of randomized controlled trials in PEDro- Physiotherapy Evidence Database in the previous one year (April 2009 to May 2010). Source: PEDro (www.pedro.org.au)

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the actual number of trials performed and stay as unpublished trials or trials published but are not yet added to PEDro.

As true it is to interpret evidence from RCT, also is true that certain guidelines be followed for standardized reporting of trial findings for better accurate dissemination of trial findings and thus effective translation into clinical practice thus facilitating evidence-based healthcare.12 Thus the EBP paradigm demands reporting of evidence to be a single-most significant factor which influences evidence-informed clinical decision-making.

The need for trial reporting guidelines- history of CONSORT statement:

The work towards formation of reporting guidelines was begun in mid 1990s which then noticed The CONsolidated Standards Of Reporting Trials CONSORT group first publishing its original version in 199613 and later revising it in 2001.14 In 2004, the CONSORT statement was extended to include reporting of harms.15 In 2008, the statement was extended with explanation and elaboration with excellent examples of reporting for use in non-pharmacological studies.16,17 The updating and publication of latest revision of the statement was done this year 2010.18 The use of reporting guidelines for various levels in a RCT (CONSORT-2010) are schematically shown as CONSORT flow diagram in figure-4.

The use of the CONSORT statement was associated with improvements in the quality of reporting RCTs when the authors compared journals which required CONSORT as mandatory versus the ones which did not.19

Hywel Williams20 added, “The benefits of CONSORT are manifest right from trial conception to the application of evidence to patients in the clinic. A trial that is “CONSORTED” gives a signal to the reader that they can find what they want to find. CONSORT 2010 is not a tool to catch out well intentioned researchers with a straightjacket of prescriptive reporting formats – it is simply an aid to ensure that a trial report contains key information. Whether you are buying a car or a trial report, you need essential information to help you decide whether it is a good one. CONSORT 2010 helps you to do that. Use CONSORT 2010 if you are a generator of research. Insist on it if you are a user of research”.

CONSORT 2010 and history revisited:

The historical “controlled” clinical trial by James Lind is depicted in the new CONSORT 2010 flowchart in figure- 5. It is now evident how a different style of reporting (description in text versus CONSORT flowchart) makes interpretation clearer for our readers.

The lack of standards of reporting (illustrated below) often undermines the value of the scientific findings which always is true. Atleast half-a-

Figure 4. CONSORT 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).19 (For a downloadable version of this diagram see the CONSORT website: www.consort-statement.org)
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Figure-5. CONSORT 2010 Flowchart of the historical Dr James Lind’s “first controlled clinical trial” in 1753. (U* - unexplained or unreported by the author).

...when half the fleet were disabled by distempers acquired by salt meats, and a long voyage without refreshments. . . . The first care then was to send the sick men ashore, which it is incredible to relate how strangely they revivified in so short a time by feeding on oranges and fresh limes. . . .”

Dominik Wujastik\textsuperscript{21} described the importance of John Fryer’s observations in India in his paper, as follows;

“Amongst the many narrative and descriptive accounts of India written by European travelers in the seventeenth century... that of John Fryer (1650–1733) stands out for its attention to daily life and the Indian environment, and especially for its many comments on the medical situation in India. Among scientifically important observations made on arrival in India, Fryer noted the value of citrus fruits in curing sailors of scurvy, predating Lind’s famous observations by half a century. Fryer travelled in India for nine years, between 1672 and 1681.”

Past is past indeed. Presently, the 20\textsuperscript{th} May 2010 marks in the pages of History, another event of highly relevant importance, The International Clinical Trials Day, at Stockholm, Sweden, organized by European Clinical Research Infrastructures Network (ECRIN) to mark the 264\textsuperscript{th} anniversary of James Lind’s first controlled clinical trial in 1747.\textsuperscript{22}
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Role of Journal of Physical Therapy:

We, the global editorial board of Journal of Physical Therapy assure you, our reader just that, of being responsive to change. We welcome articles that would bring a change, to move Physical Therapy forward, in lines of World Physical Therapy 2011 (WCPT). Every article in JPT will have a key points tab where past-information what already exist on the topic; present-information provided by this article; future- what implication the article has towards “moving Physical Therapy forward”. JPT editorial policy makes it mandatory for all submitted clinical trials to follow CONSORT 2010 statement- the CONSORT checklist for abstract and report, and flow diagram for trial procedure. JPT will also ensure unbiased publication of well-reported trials irrespective of their findings and direction of treatment-effect.

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Reviewer- R. Selvam
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REFERENCES

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Key points:

Past- The first clinical trial was performed by Dr James Lind on sailors with Scurvy and he found lemons and oranges were effective in curing the disorder. The CONsolidated Standards Of Reporting Trials (CONSORT) statement was formed in 1996, and was revised in 2001 and then extended to non-pharmacologic interventions.

Present- The CONSORT statement is revised this year 2010 with updated reporting guidelines. The randomized controlled trials (RCTs) in physical therapy are increasing at the rate of 3 studies getting added to physiotherapy evidence database (PEDro) everyday.

Future- To improve evidence-based healthcare and evidence-informed decision-making in physical therapy, the Journal of Physical Therapy (JPT) endorsed the CONSORT 2010 statement and mandated the statement and its flow diagram for future intervention studies submitted to JPT.
Appendix 1- CONSORT 2010 Checklist for randomized trials.

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

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