Deliverable number D3.6

“Evidence- and consensus-based guidance for the design, conduct and reporting of paediatric CTs (2)”

Lead Beneficiary
Sick Kids

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Reference WP
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Reference Activity
Task 3.01 – Develop standardized sets of relevant outcome measures in paediatric research.
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**Reviewers**

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*W= research on topic, writing guideline  
C= participating in conference calls  
R= reviewing drafts and final deliverable*
Abstract
In this document we present the methods used to develop a GRiP tool for selecting, measuring and reporting outcomes in paediatric phase II and III clinical trials at the study design and reporting stage. The purpose is to assist clinical trialists to systematically select, measure and report outcomes for phase II and III drug trials in paediatric populations.

Evidence now demonstrate that children are not young adults [1]; their response to treatment differs significantly due to their distinctly different anatomical, physiological and pharmacological make up. With this increased encouragement of more trials conducted separately in children [2-6], it is also being recognized that the outcomes of intervention in children are different from adults and therefore the methodology behind selecting and measuring outcomes is distinctly different from adults as well [7].

Due to the lack of age-appropriate and validated outcome measures, clinical trials performed in children have led to inconclusive results, leaving children, families, physicians, regulators and industry uncertain about the efficacy and safety profiles of many drugs. This is clearly unethical and unacceptable.

Appropriately selecting and measuring outcomes in paediatric phase II drug trials to achieve the best possible chance of success for a confirmatory phase III study in a particular disease and treatment setting is challenging but critical. Ensuring the methodology for selecting and measuring outcomes is uniform and systematic is important for all stakeholders involved in the decision making process. To date, very little work has been done to address the appropriate choice of outcomes in clinical research with children; in most paediatric specialties no research has been undertaken to develop validated outcome measures. Among those generic guidelines that address the choice of outcomes [8, 9], none have focused on phase II and III drug trials. The heterogeneity in outcome selection has impaired the synthesis of evidence in systematic reviews, therefore, led to a situation where child health decisions on treatment of children lack the appropriate underpinning evidence, and a subsequent inability to reach a consensus on the effectiveness and safety of a treatment in a paediatric population.

Clinical trialists and paediatric researchers need to be aware and equipped with tools to select valid, reliable, feasible and responsive outcomes for treatment effectiveness. The current deliverable aims to contribute to the greater GRiP goal to standardize outcome selection and measurement at the design level of paediatric phase II and III drug trials and its reporting at the time of publication of its results. The purpose of this GRiP task is to provide a tool or guidelines for clinical trialists, to rigorously select and measure validated outcomes in future paediatric clinical trials.
Research questions

1) What frameworks, guidelines or tools are currently available for selection, measurement and reporting of outcomes in the design and reporting of paediatric drug trials?
   a. Is there a focus on children?
   b. If not, can these initiatives be adopted for children?

If there aren’t any current paediatric frameworks being used then:

2) What guideline should be followed when selecting, measuring and reporting outcomes in the design and conduct of paediatric phase II and III drug trials?
**Introduction**

Children's response to treatments differs significantly from adults due to their distinctly different anatomical, physiological and pharmacological make up. Evidence now demonstrate that children are not young adults [1]; their response to treatment differs significantly based on their age, developmental stage, developmental size and other factors [2-6], it is also being recognized that the outcomes of intervention in children are different from adults and therefore the methodology behind selecting and measuring outcomes is distinctly different from adults as well [7]. Due to the lack of age-appropriate and validated outcome measures, clinical trials performed in children have led to inconclusive results, leaving children, families, physicians, regulators and industry uncertain about the efficacy and safety profiles of many drugs. This is clearly unethical and unacceptable.

There is a further complexity in relation to phase II and III drug trials in children. The therapeutic exploratory phases of new drug trials (e.g. phase II) explore their safety and potential clinical benefit in humans. Among other roles, the results of phase II studies provide the basis for confirmatory study design including selection of study outcomes for the next phase of the trial (EMA CPMP/ICH/291/95). The drug’s final approval through a regulator’s market authorization and the adoption of new therapeutic regimens by the clinical community are usually based on results from these phase III confirmatory trials. A large proportion of successful phase II drug trials fails in phase III [10]. This is frequently based on insufficient attention to dose-finding, selection of an inappropriate target population or safety concerns that arise during or after the study. About half of failures to move from Phase II to Phase III are due to problems with “efficacy”. This may mean that the drug may not actually have the intended effect. Another contributor to this high failure rate is likely to be “inadequate” attention to the selection of outcomes during Phase II - providing limited or even misleading information regarding the efficacy of the test agent. There are also increasing challenges as the trial moves from demonstrating “efficacy” using surrogate endpoints (that justify the pivotal trials) towards demonstrating “efficacy” using clinically important endpoints (that justify licensing / marketing authorisation). A further complication is that when we speak of children, we consider a wide age range, varying from neonates to adolescents, with each stage of development involving markedly different treatment dosage, route, and duration requirements and associated responses to treatments, measured using age and developmental stage appropriate outcomes [1]. Therefore, ensuring the methodology for selecting and measuring outcomes is uniform and systematic is important for all stakeholders involved in the care of children. To date, very little work has been done to address the appropriate choice of outcomes in clinical trials in children.

In a systematic review of phase II and III studies of advanced solid malignancies, Zia et al. found that approximately 60% of the drug trials in oncology that were proven “successful” in phase II failed in phase III (1). A major contributor to this high failure rate was an “inadequate” phase II trial design including the selection of outcomes that provides limited or even misleading information regarding the efficacy of the test agent. E.g., tumor regression endpoint commonly used in oncology phase II trial may not translate to clinical benefit and positive response to other markers of progression of the disease, such as progression-free survival (PFS) and/or time to progression (TTP) in phase II predicts the success of phase III trials (2).

Some outcomes in exploratory trials are about go – no go decisions, using outcomes to identify studies that are worthy of further investment. While surrogate outcomes utilized in exploratory trials present specific advantages in this phase of drug development, they are, unfortunately, not always validated for their value in predicting clinical benefit, and therefore often do not translate into clinical outcomes that are relevant to the patient and the decision makers, such as national...
competent authorities who grant marketing authorizations (licenses / labels), health care providers and payers. However, surrogate outcomes are not the only outcomes in early phase clinical trials (see section 3.1.3.2 of ICH E8). Selection of dosage regimens etc. may be based on outcomes that are not intended to be reflected in pivotal trials and are not intended to reflect clinically meaningful outcomes.

Phase II and III drug trials must be designed, performed and reported to allow accurate interpretation of results and to obtain the best quality data to facilitate and inform unbiased decisions regarding the subsequent development of the drug(s) under study in the phase III setting. This go/no go decision is particularly important since phase III trials involve large number of patients and are expensive and time consuming.

**Problem statement**

Although guidance exists for specific elements of phase II and III design, such as when to incorporate randomisation and broad design categories, there is little information to assist trialists and clinicians in choosing outcomes. Unfortunately, the quality of description of outcomes in current paediatric clinical trial protocols and reports is remarkably poor. A systematic review in neonatology trial has demonstrated that paediatric clinical trials often failed to specify a primary outcomes [11]. To date, very little work has been done on the guidance of appropriate outcome selection in paediatric clinical trials. None of the available literature provides a contemporary practical guide for outcome selection in phase II and III paediatric drug trials.

**Scope of GRiP deliverable 3.06**

In this project we will focus on one aspect of outcome selection: outcomes that are shared between exploratory and confirmatory trials. This is a small subset of the overall issue of selecting outcomes in exploratory and confirmatory trials. When an outcome is intended to be shared between stages of drug development, inappropriate selection and measurement of the outcomes can lead to waste in clinical research. This seems particularly important in paediatric clinical trials due to existing trends towards adopting outcomes from adult trials to be measured in young children, without evaluating their validity, feasibility, responsiveness and qualification in the relevant age group [8]. We will focus on outcomes relevant to marketing authorizations as trials that inform decisions about reimbursement and comparative effectiveness will use different outcomes such as number of hospital visits. Notwithstanding all the influences on outcome selection for exploratory trials outlined above, there are some development programs that do have outcomes shared between exploratory and confirmatory trials. In these programs the exploratory trials could contribute to meaningful outcomes.

GRiP deliverable (3.06) aims to contribute to the greater GRiP goal by creating avenues towards standardizing outcomes selection and measurement, at the design stage of paediatric exploratory and confirmatory drug trials, and reporting of outcomes at the time of publication. Since the focus of phase I pharmacology trials is to determine tolerance and drug toxicity with pre-defined pharmacological outcomes, our tool will not focus on phase I trials. Moreover, various research groups such as TORCH, OMERACT, COMET have been working on the development of guidelines on outcome selection in phase IV trials. Therefore the efforts will not be duplicated here for developing guidelines on outcome selection in paediatric clinical trials in phase IV.
Methods
In collaboration with the WP3 managing group, the following three phase research agenda is agreed for GRiP Task 3.01, deliverable 3.06.

PHASE I: Regulatory and Scientific Guidance
Objectives
I. to identify and critically appraise published guidance on outcome selection in paediatric drug trials
II. to identify and critically appraise published guidance on outcome selection in adult drug trials and investigate its applicability in paediatric exploratory and confirmatory drug trials

Methods
A scoping review was performed to identify existing guidelines on outcome selection in paediatric drug trials. A first step is to identify existing guidelines from regulators (e.g., WHO, FDA and EMA) and other sources (e.g., OMERACT) on the choice of outcomes in adult drug trials will also be included to explore their utility in paediatric exploratory and confirmatory phase of drug trials. The purpose of searching for adult guidelines to select and measure outcomes is to develop a starting point or template to amend these tools in paediatric drug trials. Google search was conducted between October 7, 2014 to October 16, 2014. The following search terms were used to identify publications pertaining to outcome measures in clinical trials: 'outcome measure in clinical trial', 'guideline for outcome measure', 'paediatric outcome measure', and 'guideline for paediatric outcome measure'.

Concurrently, a brief targeted literature review was performed in MEDLINE using the Ovid interface (1946 to November Week 2 2014) for guidelines for outcome selection specific to phase II and III trials to ensure no key documents were missed. The keywords used were: outcome$.ti and phase II or phase III or clinical trial$.ti. The search was limited to English language. Currently, evidence is being synthesized from the identified literature. The output of the phase I will be a short and clear draft of minimum standards and recommendations for selection, measurement and reporting of outcomes in phase II and III of paediatric drug trials. Before this preliminary tool will be applied to the empirical evidence gathering in phase II and III drug trials, the applicability of this tool will be appraised by stakeholders from the industry and regulators such as FDA and EMA.

PHASE II: Empirical Evidence Gathering
Hypothesis
We hypothesize that outcomes that are used in both exploratory and confirmatory trials that support decisions about efficacy (for example marketing authorizations / licensing) are more likely to predict positive confirmatory trials if the exploratory trial contributes to the validation and qualification of the outcomes.

Objectives
i) to investigate the “reported rationale” for the selection of outcomes that are shared between exploratory and confirmatory phase of the study;
ii) to explore which characteristics of outcome selection methods in exploratory studies might be predictive of the success or failure of subsequent confirmatory studies in children that use similar outcomes in exploratory and confirmatory trials.
Methods
We will develop four case studies in four therapeutic areas, namely oncology, neurology, rheumatology and neonatology. We will identify two pairs (one each of success and failure) of studies of exploratory and confirmatory paediatric drug trials. A study pair will be labelled as “success” if the results of both exploratory and confirmatory trials are positive. A study pair will be labelled as “failure” if the result of the exploratory trial are positive, however that of the confirmatory trials are negative.

The pair of studies will be identified from published literature or reported as protocols in EMA Paediatric Investigation Plans (PIPs) or in EPAR, FDA, or by contacting industry or regulators. We will first identify a confirmatory trial study in order to identify preceding exploratory study for inclusion.

Inclusion / Exclusion Criteria:
We will retrieve studies which are:

a. drug trials
b. focusing on paediatric population aged 0-18 years
c. in either exploratory or confirmatory phase
d. in one of the four therapeutic areas: oncology, neurology, rheumatology or neonatology
e. describing the selection of primary outcomes (in enough detail)
f. only those pairs of studies using identical chemotherapy regimens will be included. Identical chemotherapy regimens are defined as those utilizing the same chemotherapeutic agents, the same administration schedule, and the same intended patient population. However, the study pair do not need to be by the same research team / same pharmaceutical industry.

Data on outcome selection and measurement will be extracted from both exploratory and confirmatory studies. Data will be obtained on following aspects of the outcomes: i) how an outcome was selected, ii) how an outcome qualified to be included in a trial, iii) what scales and tools were used to measure an outcome including identification of validated instruments. The results regarding efficacy and safety of the exploratory and confirmatory phase will be compared. We will use this data to test the hypothesis. The results of the hypothesis testing will inform further steps.

PHASE III: Tool Development
Objective
To develop a checklist of minimal set of items to consider when selecting, qualifying, measuring and reporting validated outcomes in exploratory and confirmatory phase of the paediatric drug trials.

Methods
The results from the evaluation of existing guidance and empirical work on the critical analysis of study pairs will be evaluated to develop a checklist of minimal set of items to consider when selecting, measuring and reporting validated outcomes that bridge between the design and conduct of exploratory and confirmatory paediatrics drug trial. Agreement / consensus on the checklist items will be achieved through a consensus teleconference with the expert panel, who will appraise its quality and validity through the modified Appraisal of Guidelines Research & Evaluation (AGREE II) instrument [12]. The original AGREE II tool is used to assess the quality of practice guidelines that evaluates the methodological rigor and transparency in which the guideline was developed. It is designed to assess new guidelines, existing guidelines and updates
of existing guidelines, and can be applied in any disease area. AGREE II consists of 23 key items with six domains namely; i) Scope and purpose, ii) Stakeholder involvement, iii) Rigour of development, iv) Clarity and presentation, v) Applicability and, vi) Editorial independence. We excluded 6 of the 23 items because they were only applicable to clinical practice guidelines and not to guidelines related to clinical research in children (see Appendix 3). The user will score each item with “yes”, “no” or “unknown”. A comments section will be provided for each item. Since there is no validated cut off score for the instrument, scores from the adapted AGREE II statement will be analyzed quantitatively, while comments will be qualitatively assessed using a thematic approach.

**Deliverables**

**Methods - 31 December 2014**

The final draft of the methods will be sent to the GRiP Consensus Network, including GRiP partners, regulators, and other stakeholders. A consensus meeting will be organised on remaining issues, if necessary.

**Final GRiP deliverable, to be finished by 30 September 2015**

The results from the empirical work and consensus meeting will be analysed and integrated into final GRiP deliverable – *a tool for selecting outcomes in paediatric phase II and III drug trial*. The final tool will be available as a web-based application.

**Knowledge Translation, to be finished by 31 December 2015**

A Knowledge Translation plan will be developed upon consultation with Knowledge Translation specialists and GRiP WP1 leaders to bring the final GRiP deliverable to the attention of the end-users and stakeholders. This is addressed by the development of training modules in which paediatricians, medical sub-specialists, trialists, clinical research associates, ethics committee members and other relevant end-users can gain expertise on this topic. Moreover, it will be incorporated in the teaching material and lecture of one of the WP1 modules for MSc Programme in Paediatric Medicines Development and Evaluation for knowledge transfer. The tool will also be published in a peer reviewed journal of paediatrics. The final GRiP deliverable will be available on the GRiP website, and downloadable for free use.
### Appendix 1: Glossary of terms

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<tr>
<th>Terminology</th>
<th>Description</th>
<th>Examples</th>
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<tr>
<td>Outcome domain</td>
<td>A relatively broad aspect of the effect of illness on a child, within which an improvement may occur in response to an intervention. In general these domains may not be directly measurable themselves, so outcomes are selected to assess change within them [6].</td>
<td>In clinical trials of children with asthma, outcome domains may include lung function, health care utilization and symptom control</td>
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<tr>
<td>Outcome</td>
<td>A measurable variable within an outcome domain. The outcome can be measured at a variety of time points, which must be clearly stated by authors of clinical trials [6].</td>
<td>(1) Absolute FEV1 expressed as change from baseline (2) Number of admissions to hospital within a six month period (3) Time to first seizure after starting an antiepileptic intervention</td>
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<tr>
<td>Outcome measurement</td>
<td>A scale, scoring system, questionnaire, or other tool used for measuring an outcome. They may be an amalgamation of more than one outcome within an outcome domain, such as a score based on a variety of symptoms. More than one outcome measure may be possible to use to represent change in an outcome [6].</td>
<td>(1) The Paediatric Asthma Quality of Life Questionnaire (2) Bristol Stool Chart</td>
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<tr>
<td>Phase II / Exploratory Trial</td>
<td>Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients. These trials are typically conducted on participants who are selected by relatively narrow criteria. Determination of dose(s) and regimen for Phase II trials is an important goal of Phase II trials. Additional objectives include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further study in Phase II or III (EMA 1998).</td>
<td>A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses by O’Connor et al. [13].</td>
</tr>
<tr>
<td>Phase III / Confirmatory Trial</td>
<td>Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate, or confirm therapeutic benefit. Further exploration of dose-response relationship; and drug’s use in wider populations, in different stages of disease, or in combination with another drug are also done during these trials. Phase III trials complete the information needed to support adequate instructions for use of the drug, and thus provide adequate basis for marketing approval (EMA 1998).</td>
<td>Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy by Hanna et al. [14].</td>
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<tr>
<td><strong>Surrogate outcome</strong></td>
<td>A surrogate outcome of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful outcome that measures directly how a patient feels, functions or survives [5].</td>
<td>Magnetic resonance imaging as a surrogate marker of disability in multiple sclerosis [15].</td>
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<tr>
<td><strong>Composite outcome</strong></td>
<td>A composite outcome in an outcome that consists of two or more different outcomes. A composite outcome is recognized when a person has experienced any one of the outcomes specified in the measure [16].</td>
<td>A composite outcome of weight velocity [changes in weight z-score for age (WAZ)] and height velocity (HAZ) [17].</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>What the body does to a medicine. Description of absorption, distribution, metabolism, excretion of the medicine [18].</td>
<td>The levels of micafungin - anti-fungal prophylaxis in immunocompromised children [ Time Frame: Prior to the micafungin infusion at hour 0, at the end of the infusion (60 min), then at 1 1/2, 2, 4, 6, 8, 10, 24, 36, 48, 60, 72, 84 and 96 hours after the start of the micafungin infusion.</td>
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<td><strong>Pharmacodynamics</strong></td>
<td>What a medicine does to the body. Description of the pharmacological effects of a medicine on the various target organs [18].</td>
<td>Hemoglobin, Reticulocyte and Neutrophil count in hydroxyurea treatment for children with sickle cell anemia [19].</td>
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## Appendix 2: Adapted AGREE II Statement for Non-clinical Guidance

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<th>Domain</th>
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<td><strong>Domain 1: Scope and purpose</strong></td>
<td>1</td>
<td>The objectives are specifically described (A1*)</td>
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<td>2</td>
<td>The population (patients, public, etc.) whom the guideline is meant to apply are specifically described (A3)</td>
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<td><strong>Domain 2: Stakeholder involvement</strong></td>
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<td>The guideline development group includes individuals from all the relevant professional groups (A4)</td>
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<td>4</td>
<td>Target users of the guideline described (A6)</td>
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<td><strong>Domain 3: Rigor of development</strong></td>
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<td>Systematic methods were used to search for evidence (A7)</td>
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<td>6</td>
<td>The criteria for selecting the evidence are clearly described (A8).</td>
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<td>7</td>
<td>The strengths and limitations of the body of evidence are clearly described (A9)</td>
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<td></td>
<td>8</td>
<td>The methods used for formulating the recommendations are clearly described (A10)</td>
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<td></td>
<td>9</td>
<td>There is an explicit link between the recommendations and the supporting evidence (A12)</td>
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<td></td>
<td>10</td>
<td>The guideline has been externally reviewed by experts prior to its publication (A13)</td>
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<td></td>
<td>11</td>
<td>A procedure for updating the guideline is provided (A14)</td>
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<td><strong>Domain 4: Clarity of Presentation</strong></td>
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<td>The recommendations are specific and unambiguous (A15)</td>
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<td></td>
<td>13</td>
<td>Key recommendations are easily identifiable (A17)</td>
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<td><strong>Domain 5: Applicability</strong></td>
<td>14</td>
<td>The guideline provides advice and/or tools on how the recommendations can be put into practice (A18)</td>
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<td>The potential organizational barriers in applying the recommendations have been discussed (A19)</td>
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<td><strong>Domain 6: Editorial Independence</strong></td>
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<td>The views of the funding body have not influenced the content of the guideline (A22)</td>
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<td></td>
<td>17</td>
<td>Conflict of interest are described (A23)</td>
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*A1 means that item 1 of the original AGREE II form is used.*
References


### Document History

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<td>Winnie Chan</td>
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<td>30-Nov-2013</td>
<td>Thivia Jegathesan</td>
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<tr>
<td>31 July 2014</td>
<td>Mufiza Kapadia</td>
<td>3rd Draft</td>
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<td>12 December 2014</td>
<td>Mufiza Kapadia, Pravheen Thuraiyajah</td>
<td>4th Draft</td>
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<td>19 January 2015</td>
<td>Mufiza Kapadia, Winnie Chan</td>
<td>Minor updates, including dates.</td>
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