Outcomes in Cochrane systematic reviews related to wound care

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**WOUND REPAIR
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Outcomes in Cochrane systematic reviews related to wound care: An investigation into pre-specification

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Outcomes in Cochrane systematic reviews related to wound care: An investigation into pre-specification

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Abstract

The choice of outcomes in systematic reviews about the effects of interventions is crucial, and dictates which data are included and analysed. Full pre-specification of outcomes is also recognised as mandatory in conducting trials to minimise the risk of outcome reporting bias. This study analyses the nature and specification of outcomes used in Cochrane Wounds (CW) systematic reviews. We identified all CW review titles associated with a protocol that was published on or before 1 October 2014 and then categorised all outcome domains and recorded whether they were primary or secondary outcomes. We then identified outcome domains used in 25% or more of the protocols, and examined their specification. Adequacy of outcome specification was assessed for five elements: outcome domain, specific measurement, specific metric used, method of aggregation, and time-points. We included 106 protocols and 126 outcome domains; 24.6% (31/126) were used as primary outcomes. Eight were used in $\geq 25\%$ of protocols: wound healing, quality of life, costs, adverse events, resource use, pain, wound infection, and mortality. Wound healing was the most completely specified outcome domain (median number of elements specified=3; interquartile range [IQR] =1-5) along with resource use (median 3; IQR 2-4). Quality of life (median 1; IQR 1-3); pain (median 1; IQR 1-3); and costs (median 1; IQR 1-4) were the least completely specified outcome domains. Outcomes are frequently poorly pre-specified in the protocols for CW reviews. The elements of metric, aggregation and time-point are rarely adequately specified. We strongly recommend that reviewers make greater efforts to specify outcomes, using the five elements. Better pre-specification of outcomes is likely to improve review quality by reducing risk of bias in data abstraction and analysis and by reducing subjectivity in the decision-making regarding which outcomes to extract; it may also improve outcome specification in clinical trial design and reporting.

Introduction

Over recent years, there has been increased focus on which outcomes are identified for measurement in randomised controlled trials (RCTs) and systematic reviews, and how and why these choices are made. An outcome can be defined as a measureable event or characteristic that is likely to reflect the impact of an intervention, whether in terms of benefits or adverse events. Examples of dichotomous outcomes include: death; wound healing and wound infection. Examples of continuous outcomes include: health-related quality of life; activity levels; weight and blood pressure (1).

Researchers conducting both study types generally *a priori* select at least one primary outcome and a number of secondary outcomes. The primary outcome(s) should be the most clinically relevant and important to patients and policy makers and, in the case of RCTs, is/are used as the basis for the calculation of needed sample size for the RCT. Secondary outcomes should also be important for decision making, but are perhaps less crucial than the primary outcome (1,2,3).

Clear pre-specification of primary and secondary outcomes is important for both RCTs and systematic reviews. Once identified primary outcomes remain the key outcome finding. This commitment to reporting the primary outcome is one element of avoiding selective outcome reporting, which leads to outcome reporting bias, which can occur when reported outcomes have been cherry picked from all those available, based on statistical significance rather than *a priori* specification. This bias has been reported as a problem in RCTs (4) as well as potentially systematic reviews (2,3). A related issue to reporting biases is that of ‘spin’ in which outcomes that are not associated with a treatment effect are down-played in reports and outcomes with statistically significant findings are made more prominent. Previous work has shown that in RCTs without a statistically significant difference in the primary outcome secondary outcomes became the focus of the reporting and are particularly highlighted in abstracts and study conclusions, including in wounds research (5,6).

Outcome pre-specification is particularly important for systematic reviews which gather data from multiple RCTs, each of which might measure a given outcome in a number of different ways. As an example, a systematic review might plan to include data on quality of life. However, this outcome can be measured in using various instruments and at multiple time points. Without further specification of the outcome there is a risk that systematic review authors would make *post hoc* decisions about which trials and outcomes provide acceptable measures of quality of life. Consequently, there may be a conscious or subconscious focus on those results that seem to demonstrate differences between treatment groups rather than those that were considered the most relevant *a priori*.

Prior research has elucidated a five-element framework of key components should be considered during pre-specification of outcomes in SRs and RCTs (7,8). Saldanha et al (7) modified the list initially proposed by Zarin et al. (8) by introducing time-point as a standalone element whereas this was previously integrated into the four other elements:

1. *Domain* or outcome title
2. *Specific measurement* or technique/instrument used to make the measurement
3. *Specific metric* or format of the outcome data from each participant that will be used for analysis
4. *Method of aggregation* or how data from each group will be summarized
5. *Time-points* that will be used for analysis

Cochrane systematic reviews are an important resource for health care professionals, patients and policy makers. Data show that systematic reviews produced by Cochrane Wounds (CW) are amongst the most highly accessed systematic reviews in the Cochrane Library (9). CW reviews cover all aspects of wound treatment and prevention as well as prevention and treatment of healthcare acquired infections including surgical site infections. There is a range of possible outcomes that can be analysed in wounds-related reviews and we wanted to explore which are most commonly used, which are most frequently specified as primary outcomes and how well outcomes are pre-specified in CW protocols. We considered a fully-specified outcome to have the five elements used by Saldanha et al (7) (Table 1).

(Insert Table 1 here)

Core outcome sets have been proposed as one mechanism to improve the consistency of outcome measurement and reporting in RCTs and SRs (1,10,11), however there is currently no core outcome set in wound care. As with the previous study (7), our aim was to explore, describe and understand how outcomes have been conceptualised and specified in wounds reviews to date. Meanwhile, we also assessed the quality of outcome specification, by using the domain, measurement, metric, aggregation and time points. The insights gained will inform future discussions about how outcomes in wound care systematic reviews can be optimally specified for both future reviews and future RCTs.

Methods

Source of data

We identified all CW review titles associated with a published protocol available on or before 1 October 2014. For these titles we then located the oldest published version of the protocol available. Where a published protocol was not available in the Cochrane Library, we requested access from the CW Managing Editor. Where a published version of a protocol was still not available we used the methods section of the most recent published review in lieu of the protocol.

How we judged and classified the specifications of outcomes based on individual RCTs

1. Extraction of outcome domains

One author (ZL) extracted a list of all outcome domains from the methods sections of eligible CW protocols (and reviews where protocols were not available– for ease all texts will be referred to as protocols from now on). The definition and grouping of domains was then checked and agreed by a second reviewer (JD) with input from a third (NC or IS) where required. We recorded whether each domain was listed as a primary or secondary outcome; where not specified we recorded them as secondary outcomes. For example: the outcomes “length of hospital stay”, “number of dressing change” and “staff time” were initially listed as three different domains by one author (ZL); then after checking by other authors (JD & NC), these outcomes were grouped under the domain of “resource use”.

We extracted the following data for included protocols: year of publication; wound type; outcome domains named; we extracted data on outcome specification for domains that appeared in at least 25% of included protocols. For each outcome domain (element 1), we extracted the named specific measurement(s) (element 2) and method(s) of aggregation (element 4), and whether or not a specific metric (element 3) and time-point (element 5) were specified in the protocol. We anticipated that some outcome domains could have multiple specific measurements/specific metrics/methods of aggregation/time-points in a single protocol. For example the domain of *wound healing* could be associated with the specific measurements of “proportion of participants with a completely healed wound” and “change in wound area.” In other words, one domain could have multiple outcome specifications. When this was the case, we looked for (and extracted) the specific measurements, specific metrics, methods of aggregation, and time-points for each outcome specification. Detailed below are our processes for data extraction for the other elements for each outcome domain.

2. Data extraction on outcome specification: specific measurement(s)

We considered specific measurement to have been specified if the review authors stated how the outcome should be measured, including (where relevant) with which instruments, tools, scales, scores, and/or how the outcome should be defined. We assessed whether the measurement had been specified and extracted the detail of the measurement(s). If methods of measurement were not pre-specified, or relevant phenomena not defined (for example, if “wound healing” was not defined), we classified the specific measurement as “unspecified” (see Table 2).

3. Specific metric(s)

We considered specific metric to have been specified if the review authors specified how they would analyse the data, including change from baseline, value at a time-point, or time-to-event. We classified the specific metric as specified or not, and noted the type of specific metric (see Table 2).

4. Method of aggregation

We considered specific metric to have been specified if the review authors specified how the data will be summarised, including the mean, median, percentage or proportion, or as an absolute number. Where review authors did not mention any aggregation way, we classified it as unclear (see Table 2).

5. Time point(s)

We noted whether the authors specified the time points to be used in their analysis. Where authors stated that this would be the “latest time point in the trial” or similar we regarded this as specified, even if one such statement was made for all outcomes in the review. The example of “time to complete healing” would be classified as “time-point specified” because time is intrinsic to the metric (see Table 2).

After initial pilot testing of our data abstraction process using 10 protocols, one investigator (ZL) then extracted data into a Microsoft Excel spread sheet for all protocols. A second investigator (JD) verified all data extraction. In order to check agreement, a third investigator (IS) and a fourth investigator (NC) independently extracted data from a randomly selected 10 protocols. All discrepancies were resolved through discussion and consensus.

(Insert Table 2 here)

Analysis

We present a descriptive analysis of the number, types and degree of specification of outcomes in the included protocols. The extent of completeness of outcome specification was assessed based on the use of the five possible elements for each main outcome domain. If all the five elements were identified for one outcome, then we labelled it as a “completely specified outcome”. We summarise the median and interquartile range (IQR) for the number of outcome elements (out of a total of five) specified for each included outcome domain and then describe the elements in more detail for each domain. We also highlighted the frequency of categories of metric, aggregation and time-points for each outcome domain.

Results

Characteristics of protocols examined and outcome domains used

We identified 106 published systematic reviews associated with Cochrane Wounds (Appendix I). We obtained the original protocols for 91 of the 106 titles (86%). We used the methods section of current reviews for the remaining 15 titles (14%). Of the 91 protocols, 85 (93%) were associated with a published completed review. Full data extraction of the number of times each outcome domain used is found in Appendix 2.

Interventions to prevent and/or treat wound infection were the most frequently addressed topic in the 106 protocols (25%), followed by leg ulcer treatments (14%), surgical wound treatments (13%), pressure ulcers (11%) and foot ulcers (10%). This classification was based on the Cochrane Library. Most of the included reviews (95/106; 90%) were published after 2000 (Table 3).

(Insert Table 3 here)

We identified 126 unique outcome domains (Appendix 3); these were used 655 times across the 106 protocols. Of the 126 outcome domains, 31 (25%) were listed as primary outcomes at least once. The top 10 outcome domains used most frequently as outcomes are reported in Table 4.

(Insert Table 4 here)

Most frequent outcomes

We then focused on the eight outcome domains that were each included in at least 25% of protocols, viz: wound healing, adverse events, wound infection, quality of life, cost, resource use, pain, and mortality (Table 5). At least one of these eight domains was included in 101/106 (95%) protocols. Across the 101 reviews these eight outcome domains were used a total of 494 times. The most frequent outcome domains were wound healing (59/101; 58%), quality of life (56/101; 55%), and costs (56/101; 55%) (Table 3). The wound healing domain (with its associated specific measures of time to healing, proportion of wounds healed and

change in size) was the most frequent domain (101 protocols – presenting 170 usages, of which 127 usages were identified as primary outcomes). The domain “costs” was also frequently used (60 instances) but never as primary outcome (Table 5).

(Insert Table 5 here)

Number of completely specified elements

We assessed the number of the remaining four possible elements specified for each of these eight outcome domains (specific measurement, specific metric, method of aggregation and time point). Each outcome specification was considered by default to have specified a minimum of one element (i.e., outcome domain). Overall, a median of two elements was specified per outcome domain. Wound healing was the most completely specified outcome domain (median 3 elements; IQR 1-5) (Figure 1). The domain of wound healing was completely specified once (29). Resource use was also highly specified (median 3 elements; IQR 2-4) (Figure 1). The most incompletely specified outcome domains were quality of life (median 1; IQR 1-3); pain (median 1; IQR 1-3); and costs (median 1; IQR 1-4). Table 2 provides some examples of outcome text and their extent of complete and incomplete specifications.

(Insert Figure 1 here)

Comparability of specification across domains

Table 6 gives more detail regarding the distribution of specific measurements (element 2), specific metrics (element 3), methods of aggregation (element 4) and time-point (element 5) across outcome domains. The patterns of completeness for individual elements were similar across the eight most frequent outcomes. Metrics and methods of aggregation were specified least often, while domains and time-points were specified more often than other elements. For example, the specific measurements for the domains of resource use and mortality were adequately specified 98% - 100% of the time. In contrast, the domain of wound healing, a key outcome in wounds research, was associated with the most poorly specified specific measurement (12%), usually because what constituted wound healing had not been defined. The specific metrics for the domains of adverse events, cost, mortality,

pain and quality of life were also poorly specified. Method of aggregation was the least well specified element (76% - 100% unclear) and when it was specified, it was usually a “percentage/proportion”. Similarly, time-points were very poorly specified except for the domain of wound healing.

(Insert Table 6 here)

Discussion

To the best of our knowledge, this is the first investigation of the nature and adequacy of specification of outcomes in systematic reviews of wounds research. The large volume of possible outcomes that can be measured and reported in wounds research makes this a particularly important area to explore.

Overview of outcome domains

We identified 126 different outcome domains specified across 106 systematic review protocols published by Cochrane Wounds. This large number partly reflects the wide range of target conditions covered by the scope of this Cochrane Review Group (which includes healthcare-acquired infections as well as wounds), but also reflects variation in outcome selection and/or reporting. We identified the most frequent eight outcome domains that were included in 25% or more of the included protocols, leaving the majority of outcome domains (n=118) being used relatively infrequently. Whilst wound healing has been recommended as the most important outcome in many cases, there is frequently focus on surrogate or interim outcome of changes in wound size (12,13). Other important outcomes include wound infection which can be defined in several different ways as pain and quality of life (12,14).

Outcome specification

In our study sample, the *specific measurement* was most often specified among the five elements of a well-specified outcome, whilst the method of aggregation and the time points of interest were the least often specified. For example, review authors often stated “wound healing” but did not specify how data would be aggregated or at what time point they were

interested in the outcome being measured. Noticeably, timing is crucial in wound healing area. Where outcome time-points of interest are not pre-specified in a systematic review, it is not obvious how data from studies with different follow-up periods would be dealt with. Wound healing outcomes measured at 4 weeks and 52 weeks are very different, and since healing is unlikely to be a linear process combining data from different time points is likely inappropriate. There is also the issue of increased risk of type 1 errors when outcomes measured at multiple time points are all analysed separately. This issue needs to be considered in more detail at the outset of reviews (12). This is an important issue that likely requires more attention in reviews due to its importance not only from the clinical perspective but also with regard to resource use and economic cost (12).

Primary outcomes tended to be better specified than secondary outcomes. Wound healing was the most frequent primary outcome and the most highly specified outcome domain with 19% instances had four or five elements as specifications. This finding echoed that of Saldanha et al. (7) where primary outcomes were the most well specified. However, there are objective definitions of healing available; for example, one review defined it as “complete epithelial cover in the absence of a scab (eschar) with no dressing required” (15). The FDA defines complete wound closure as “skin reepithelialisation without drainage or dressing requirements, confirmed at two consecutive study visits two weeks apart, and the time should be specified when being analysed” (13). None of the review protocols we scrutinised used the FDA definition or Ashby definition. Secondary outcomes such as pain, quality of life and cost were usually the least-well specified elements. These are outcomes that are widely measured using a vast number of approaches including some that are well-validated and others that are not. Quality of life was also the most poorly specified outcome domain in Cochrane reviews in the field of eyes and vision (7) as well as one of the outcome domains also not well specified in RCTs (8).

Implication of findings

It is accepted practice that target outcomes for randomised controlled trials are fully specified in trial protocols. The same requirement should apply to systematic reviews. It has been suggested that outcomes may be poorly pre-specified for systematic reviews because reviewers tend to be responsive to the outcomes that have been reported by trialists and

that full outcome specification is a rather novel idea in the systematic review community (7). There is also a sense that reviewers will be aware of the way outcomes are typically reported in RCTs (indeed they are part of the same community) and will be reluctant to specify outcomes too highly *a priori* with the consequent risk of reducing the volume of data or missing something “important”. Our findings together with these possible explanations suggest that there is value in developing core outcome sets in the field of wounds as there have been in other areas (11,16,17). Core outcome sets refer to the minimum set of outcomes that should be measured in clinical trials in a given field (17). Our search of the COMET Database on 1, Jan, 2016 revealed the non-existence of a core outcome set for research addressing wound care. We believe the wounds research, clinical practice, and patient communities will greatly benefit from having agreed sets of outcomes that are considered important. This would enable an examination and comparison of the effectiveness of clinical interventions based on a common set of outcomes.

The development of core outcome sets involves a consensus process. The process to define outcome measures is data-driven, iterative, and prepared by expert working groups, including patients, wound specialists, health professionals, trialists, methodologists, scientists from industry, regulators (9). A final consensus is formulated based on all participants’ views and preferences (9). Our study, by documenting the most frequent outcome domains and their degree of specification, could provide a useful starting point for development of core outcome sets for wounds research. It is likely that different outcome sets will be needed for different wound types (for example those healing by primary vs. those healing by secondary intention). Wound healing as a domain is difficult to apply to surgical wounds healing by primary intention because it is difficult or impossible to define or identify *when* wound healing occurs and more valid and relevant to count problems with wound healing (such as infection or dehiscence).

Finally, development of core outcome sets and full pre-specification of outcomes play an important role in reducing bias in systematic reviews. Such approaches help to reduce outcome reporting bias by: (i) preventing selection of outcomes into reviews based on the direction or significance of the results, and (ii) preventing the inclusion of outcomes based on knowledge of those that have been included in RCTs rather than those that are known to

be important to decision makers (9,10). Authors of future systematic reviews are strongly encouraged to follow this methodological guidance regarding to outcomes to conduct a high quality review.

There is a growing recognition that insufficient attention has been paid to the outcomes measured in clinical trials and systematic reviews of randomised trials. The usefulness of the studies is compromised by inconsistency in the outcomes assessed across the different studies. The development of core outcome sets is one response to this problem. We strongly recommend that authors of systematic reviews make greater efforts to specify in detail, at the protocol stage, all outcomes of interest using the five elements of a completely specified outcome (domain, specific measurement, specific metric, method of aggregation, and time-points). This will finally reduce bias in data abstraction and analysis in systematic review and ultimately, make more efficient usage to decision-makers.

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Figure 1: Completeness of outcome specification for the 8 most frequent domains (median number of specified elements (interquartile range))

Element	Example
1. Outcome domain or outcome title	e.g. wound healing
2. Specific measurement or technique/instrument used to make the measurement	e.g. time to complete wound healing (healing as defined by trial authors)
3. Specific metric or format of the outcome data from each participant that will be used for analysis	e.g. change in wound area from baseline
4. Method of aggregation or how data from each group will be summarized	e.g. mean change in wound area from baseline
5. Time-points that will be used for analysis	e.g. at maximum follow-up

Table 1: Wounds-related examples of five elements of a completely specified outcome (7)

Verbatim outcome text from protocol	Outcome domain	Specific measurement	Specific metric	Method of Aggregation	Time point	Number of specified elements (out of five)
Time to complete wound healing	Wound healing	Not specified	Time to event	Not specified	Specified	3
Proportion of wounds completely healed	Wound healing	Not specified	Value at a time-point	Percentage/proportion	Not specified	3
Rate of change in wound volume	Wound healing	Not specified	Change in size	Not specified	Not specified	2
Adverse reactions (e.g. anaphylaxis, gastro-intestinal or skin rash)	Adverse event	Adverse reactions (e.g. anaphylaxis, gastro-intestinal or skin rash)	Not specified	Not specified	Not specified	2
Incidence of infection	Wound infection	Not specified	Value at a time-point	Not specified	Not specified	2
Length of hospital stay (at maximal follow-up)	Resource use	Length of stay	Change from baseline	Not specified	Maximal follow-up	4
All-cause mortality at maximal follow-up	Mortality	Yes	Value at a time-point	Unclear (if not specified)	Maximal follow up	4
Quality of life measures (based on any item from a validated scale, e.g. SF-36, EuroQoL, WHOQOL-BREF (Asnani 2009))	Quality of life	SF-36, EuroQoL, WHOQOL-BREF	Not specified	Not specified	Not specified	2

Table 2: Examples of outcome specification

	Number of protocols (% , n) Total N = 106	Number of outcome domains per protocol by category and Median (IQR)
Clinical topic in CW library		
Prevention/treatment of wound infection	25% (27)	6 (IQR 4-7)
Leg ulcers	14% (15)	6 (IQR 4-7)
Surgical wounds	13% (14)	6.5 (IQR 6-8)
Pressure ulcers	11% (12)	5 (IQR 4-6)
Foot ulcers	10% (11)	6 (IQR 5-8)
Burns	7% (7)	7 (IQR 5-9)
Wound drainage	6% (6)	9 (IQR 8.5-12)
Chronic wounds	3% (3)	5 (IQR 4-6)
Acute wounds	2% (2)	3.5 (IQR 2-5)
Mixed wounds	2% (2)	7 (IQR 5-9)
Both chronic and acute wounds	0.9% (1)	6 (IQR 5-8)
Other	6% (6)	4.5 (IQR 3-7.5)
Year of publication		
≤2000	11% (10)	5 (IQR 3-6)
2001 to 2005	27% (26)	6 (IQR 4-9)
2006 to 2010	32% (30)	6 (IQR 5-8)
2011 or later	36% (34)	6 (IQR 5-7)

Table 3: Number of protocols and outcome domains by clinical topic and year published

Most frequently used outcome domains (for primary outcome) in all 106 protocols	Frequency of domains included in 106 protocols - n (%)	Frequency as primary outcome - n
Wound healing	59 (56%)	46
Quality of life	56 (53%)	8
Costs	56 (53%)	0
Adverse events	50 (47%)	12
Resource use	46 (43%)	1
Pain	39 (37%)	2
Mortality	31 (29%)	12
Wound infection	27 (25%)	18
Recurrence	20 (19%)	3
Surgical site infection	16 (16%)	15
Amputations	13 (12%)	5
Wound dehiscence	8 (8%)	5

Table 4: Frequency of outcome domains in all 106 protocols and whether specified as primary outcome

Eight domains included in ≥25% of protocols (total = 101)	Frequency of domain in 101 protocols* (% in the total 494 times)	Frequency as primary outcome (% in the total 494 times)
Wound healing	170 (34%)	127 (26%)
Wound infection	32 (6%)	20 (4%)
Pain	43(9%)	5 (1%)
Resource use	49 (10%)	1 (0.2%)
Cost	60 (12%)	0 (0%)
Adverse events	52 (11%)	12 (2.4%)
Mortality	32 (6%)	12 (2.4%)
Quality of life	56 (11%)	8 (1.6%)

Table 5: number of instances of eight domains used in 25% or more of protocols

* Can be more than 101 because one domain may have several associated specific measurements, each with its own specific metric, method of aggregation and time point).

Domain	<i>Specific measurement</i> (element 2) – Specified vs. not		<i>Specific metric</i> (element 3) – Actual metric				<i>Method of aggregation</i> (element 4) – Actual method				<i>Time-points</i> (element 5) – Specified vs. not	
	Specified	Unspecified	Value at time point	Time to event	Change from baseline	Unclear	Mean/m edian	Per cent/ proportion	Absolute number	Unclear	Specified	Unclear
Wound healing	12%(21)	88% (149)	36% (62)	34% (57)	16%(27)	14%(24)	–	24% (41)	–	76% (129)	48% (82)	52%(88)
Adverse events	58% (30)	42% (22)	8% (4)	–	–	92% (48)	–	2% (1)	–	98% (51)	4% (2)	96%(50)
Wound infection	66% (21)	34% (11)	50% (16)	3% (1)	–	47% (15)	–	–	–	100% (32)	9% (3)	91%(29)
Resource use	98% (48)	2% (1)	–	–	41(84%)	16% (8)	–	–	–	100% (49)	8% (4)	92%(45)
Cost	42% (25)	58% (35)	3% (2)	–	–	97% (58)	–	–	2% (1)	98% (59)	2% (1)	98%(59)
Mortality	100% (32)	–	13%(4)	–	–	88% (28)	–	–	–	100% (32)	13% (4)	88%(28)
Pain	42% (18)	58% (25)	2% (1)	–	–	98% (42)	–	–	–	100% (43)	2% (1)	98%(42)
Quality of life	43%(24)	57%(32)	2% (1)	–	2(4%)	95% (53)	–	–	–	100% (56)	5%(3)	95%(53)

Table 6: Frequency of categories of metric, aggregation and time-points by domain