Range and heterogeneity of outcomes in randomized trials of pediatric chronic kidney disease

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Abstract

Objective: To determine the range and heterogeneity of outcomes reported in randomized controlled trials (RCTs) of interventions for children with chronic kidney disease (CKD).

Study Design: The Cochrane Kidney and Transplant Specialized Register was searched to March 2016. Randomized trials involving children across all stages of CKD were selected. All outcome domains and measurements were extracted from included trials. The frequency and characteristics of the outcome domains and measures were evaluated.

Results: From 205 trials included, 6158 different measurements of 100 different outcome domains were reported, with a median of 22 domains per trial (interquartile range [IQR] 13 to 41). Overall, 52 domains (52%) were surrogate, 38 (38%) were clinical, and 10 (10%) were patient-reported. The five most commonly reported domains were blood pressure (76 [37%] trials), relapse/remission (70 [34%]), kidney function (66 [32%]), infection (61 [30%]), and height/pubertal development (51 [25%]). Mortality (14%), cardiovascular disease (4%) and quality of life (QOL) (1%) were reported infrequently. The two most frequently reported outcomes, blood pressure and relapse/remission, had 56 and 81 different outcome measures, respectively.

Conclusions: The outcomes reported in clinical trials involving children with CKD are extremely heterogeneous and are most often surrogate outcomes, rather than clinical and patient-centered outcomes such as cardiovascular disease and QOL. Efforts to ensure consistent reporting of outcomes that are important to patients and clinicians will improve the value of trials to guide clinical decision-making. In our study, non-English articles were excluded.

Introduction

Since the recognition of children as "therapeutic orphans" in the 1960s,(1) there has been a wave of international efforts to improve trial-based evidence to support the use of health interventions in the pediatric setting.(1-12) The past two decades has seen an increase in the number of trials conducted in children since the United States and Europe revised legislation on labelling of medicines to mandate pediatric data.[3] Also, major pediatric trial networks have been established globally, including the US National Institute of Child Health and Human Development Pediatric Trial Network and the Network of Pediatric Research at the European Medicines Agency, to improve infrastructure and capacity for pediatric trials.(13, 14)

Despite this upsurge in pediatric clinical trials, the relevance and value of trials may be limited by problems in the prioritization, design, reporting and dissemination of research, including outcomes measured and reported.(15-21) Trials are only as informative as their outcomes,(22) yet many report outcomes that may not be directly relevant to patients and clinicians, and do not involve children and caregivers in the selection of outcomes.(23-25) Analyses of pediatric trials within specific health conditions have shown that the outcomes reported are extremely variable, including the definitions and measures used(23-27), which limits comparability of the effectiveness of interventions across studies.(16) Initiatives to establish core outcomes, to be reported at a minimum in all trials with specific health condition, such as The Outcome Measures in Rheumatology (OMERACT), have demonstrated improvement in the relevance and reporting of outcomes in trials,(22, 23, 28-30) though core outcome sets are generally lacking in the pediatric setting.

Children with chronic kidney disease (CKD) have a mortality rate up to 30-times higher than the age-matched general population, and those who progress to end-stage kidney disease depend on

dialysis or a kidney transplant for survival.(31, 32) Although many trials have been conducted in children with CKD, the risk and prevalence of comorbid conditions, treatment complications, developmental problems, debilitating symptoms, such as fatigue, and impaired quality of life (QOL) remain high.(33-44) Improvements in health care and outcomes through research rely on the relevance and consistency of outcomes reported in trials in this vulnerable population. Affected children depend on their caregivers and clinicians to provide long-term, complex, and highly technical treatments that have profound implications for their development and well-being. We aimed to describe the scope and consistency of outcome domains and measures in trials involving children with all stage of CKD, to inform strategies for establishing core outcomes that are important to children, families and clinicians to be reported in trials, to inform clinical decision making and ultimately to improve the outcomes for children with CKD.

Methods

Selection criteria

We searched the Cochrane Kidney and Transplant Specialized Register for all randomized controlled trials (RCT) involving children aged up to 21 years or less (the upper age limit to define the pediatric population is up to 21 years in the United States(45)) with any CKD diagnosis and at treatment stage (CKD Stage 1-5 [not on renal replacement therapy], 5D [hemodialysis or peritoneal dialysis] and 5T [kidney transplant]) up to March 2016 (Figure 1 (online)). We used search terms relating to children and pediatrics. Trials that included more than 50% of patients aged above 21 years were excluded. Trials that included children with chronic conditions, but did not report data from the CKD population, were not eligible.

Data extraction

We extracted the following trial characteristics from each trial: publication year, setting (participating countries), sample size, mean age of participants, study duration, intervention type, and all outcomes. We defined outcome measures as any measures reported separately for all trial arms. We extracted all specifications of the outcome measures, if reported, including the: outcome domain (e.g. blood pressure), specific measurement (e.g. percentage of hypertensive patients), method of aggregation (e.g. percentage change), specific metric (between commencement and end of the trial), and time point of measurement (defined as the time frame from trial commencement to when the outcome was measured).(46)

Analysis

We categorized all the outcome measures from all the included trials into outcome domains. The first author (LC) drafted the initial list of outcome domains. This was cross-checked by four reviewers and revised until consensus was achieved (AT, BS, GR, JCC). The outcome measures were then grouped according to the final list of outcome domains, which was re-reviewed by the same four reviewers. All outcome domains were further categorized as surrogate (biochemical or physiological outcomes i.e. pathophysiological manifestations of health conditions, including such as blood pressure(47)), clinical (medical outcome of a condition or treatment), and patient-reported (outcomes reported on by patients and caregivers, typically related to how the patients function or feel in relations to a health condition or therapy), based on standard nomenclature.(48),(49) Some outcome domains included measures that straddled several categories – surrogate, clinical and patient-reported. Thus, classification of the domains was based on the largest proportion of outcome measures. The number of trials, and dialysis- and transplantation-specific trials that reported each outcome domain were calculated.

We conducted a detailed analysis of outcome measures of the three outcome domains in each category that were reported most frequently across trials, as well as the three pediatric-specific domains (height and pubertal development, weight/BMI/body composition and school performance). The measurement, aggregation, metric and timing as reported in the primary studies were analyzed. We retained the original term if studies did not further define or provide details on the outcome measure. Statistical analyses of frequency were conducted using R *version 3.2.3* (R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org/).

Results

Characteristics of trials

Our search yielded 1266 trials, of which 205 included 2174 children with CKD (Table 1). The trial characteristics are shown in Table 1. Overall about half of trials involved children with CKD Stage 1 to 5 (123 [52.1%] trials), 32 [13.6%]) trials involved patients on hemodialysis, 40 [16.9%] involved peritoneal dialysis, and 41 (17.4%) involved kidney transplant recipients. The setting of the trials spanned 43 countries, including the United States (51 [25%] trials), India (18 [9%]), Japan (15 [7%]), Germany (14 [7%]), and England (14 [7%]); and 28 (14%) trials were multinational. The trials were published from 1970 to 2015. The median trial duration was 12 months (interquartile range [IQR] 6 to 24 months), and the median sample size was 40 patients (IQR 22 to 76 patients), with only six (2.9%) larger than 200.

Outcome measures and outcome domains

Across 205 trials, 6158 outcome measures were reported. The number of outcome measures per trial (including time points of measurement) ranged from 1 to 145, with a median of 22 per trial (IQR 13 to 41). The number of unique outcome measures per trial (excluding time points) ranged

from 1 to 64, with a median of 15 (IQR 9 to 26). We excluded 382 outcome measures because they were not a direct health outcome measured in patients (e.g. “mean cold ischemia time,” and “medication dose/use/duration”) or were specific to a single intervention within a trial (e.g. “number of patients monitored and educated”). The remaining 5776 were classified into 100 outcome domains and these were grouped into: surrogate (52 [52%]), clinical (38 [38%]) and patient-reported outcomes (10 [10%]) (Table 2, 3, 4; online). Nine outcome domains were specific to transplantation, and four were specific to dialysis.

Frequency of outcome domains reported in trials

Figure 2 depicts the proportion of trials that reported each outcome domain. The six most commonly reported outcome domains were: blood pressure (76 [37.1%] trials), relapse/ remission (70 [34.1%]), kidney function (66 [32.2%]), infection (61 [29.8%], height/pubertal development (51 [24.9%]) and weight/body mass index/body composition (50 [24.4%]). Mortality and cardiovascular disease were reported in 28 (13.7%) and 8 (3.9%) of trials, respectively. Depression and QoL (global) were reported in 2 (1.0%) of trials, and school performance was reported in 1 (0.5%) of trial. Table 5 details the proportion of trials that reported the 10 most frequent outcome domains, and the proportion of trials reporting each outcome domain.

The number of trials that reported a minimum of one surrogate outcome domain was 180 (87.8%), and 164 (80.0%) and 49 (23.9%) reported at least one clinical and one patient-reported domain, respectively. From the 30 (30%) outcomes reported by at least 10% of trials, 17 were surrogate, 12 were clinical and one was patient-reported.

Outcome measures and time points

Figure 3 shows the number of outcome measures and time points of measurement for 10 outcome domains (the three most frequently reported surrogate and clinical outcome domains, two most frequently reported patient-reported domains, and two pediatric-specific domains). The outcome measures and time points of measurement for each outcome domain listed in Figure 3, excluding "school performance" are shown in Figure 4a-i; online.

The three most frequently reported surrogate outcomes were "blood pressure" (56 outcome measures [168 including different time points]; Figure 4b; online), "relapse/remission (82 [240 including time points]; Figure 4c; online) and "kidney function" (47 outcome measures [173 including time points]; Figure 4a; online). The clinical outcomes of "infection", "height and pubertal development" and "dermatologic disorder" had 114 (165 including time points), 34 (137 including time points) and 24 (52 including time points) different outcome measures, respectively (Figure 4d-f; online). For patient-reported outcomes, "pain" (Figure 4g; online) and "psychological impact" (Figure 4h; online) had 27 (50 including time points) and 10 (15 including time points) measures, respectively. There were two pediatric-specific outcomes, "weight/body mass index/body composition" and "school performance". The former had 40 (114 including time points) (Figure 4i; online), and the latter had only one outcome measure, at one time point.

Characteristics of primary outcomes

Across the 205 trials, 109 (53.2%) did not specify the primary outcome, 68 (33.2%) specified several outcomes as primary outcomes, and 28 (13.6%) specified one unique primary outcome. The outcomes specified as primary outcomes corresponded to 36 different outcome domains: 24 (66.7%) were surrogate outcomes, 10 (27.8%) were clinical outcomes and 2 (5.6%) were patient reported outcomes. The 6 most frequently reported primary outcomes were "relapse/ remission" (43 [44.8%] trials), "proteinuria, albuminuria" (22 [22.9%] trials), "kidney function" (18 [18.8%] trials), "height and pubertal development" (15 [15.6%] trials), "anemia/hemoglobin/iron" (9

[9.4%] trials) and bone density/markers" (6 [6.3%] trials). Table 6; online details the primary outcome domains, and the proportion of trials reporting each one.

Discussion

Biochemical surrogate outcomes comprised over half of the outcome domains reported in clinical trials involving children with CKD with blood pressure, kidney function, weight and urine protein being the most frequently reported. These were much more common compared with clinical and patient-centered outcomes such as mortality (14%), cardiovascular disease (4%), and QOL (1% of trials). In terms of pediatric-specific outcomes, physical development (height and pubertal development, weight/BMI/body composition) were reported in more than 25% of trials, but school performance was assessed in only one trial. Thus, the relevance of current trials to guide treatment decisions based on outcomes that are important to children with CKD and their caregivers may be disputable. Also, there is wide heterogeneity of outcome domains reported across trials and, within each outcome domain, large variability in the definitions, time points, and measures used. Such inconsistencies in outcome reporting obscure assessments about the comparative effectiveness of interventions across trials.

Surrogate outcomes, such as serum biomarkers, are frequently used in trials because they require a smaller sample size, shorter time-frame, and fewer resources to evaluate treatment effectiveness. These may be key considerations given the relatively small population of children with CKD, and the additional ethical and logistical requirements to conduct trials in children. However, surrogate outcomes have not been robustly validated in this setting and do not bear direct relevance to patients and their families. Serum phosphate, serum calcium, parathyroid hormone and anemia/hemoglobin/iron were reported in more than 15% of trials but there is no evidence to indicate that they predict mortality and cardiovascular events in patients with CKD.(49-55) While some physiological markers may be appropriate measures of short-term disease activity for acute

conditions,(56) they are arguably less informative in chronic conditions. Further studies are needed to validate surrogate outcomes such as parathyroid hormone, serum phosphate and serum calcium.

Many outcomes that have been identified as important and clinically relevant to children with CKD were absent in most trials. Studies that have directly elicited perspectives from children living with CKD have identified their priorities as school attendance and performance, anxiety, social participation, ability to participate in physical activity, hospitalization, and fatigue.(42, 56-61) However, patient-reported outcomes constituted only 10% of all outcome domains reported, and were infrequently reported. Psychological problems, including depression, were reported in less than 10% of trials. School performance, fatigue, physical function and QOL were reported in just 1% of trials. No trials reported on social participation. The omission of outcomes important to children with CKD can hamper efforts to implement interventions and strategies to optimize outcomes that are meaningful to patients themselves. Further work is needed to identify dimensions of QOL that are important to patients and subsequently develop feasible and validated measures to use in trials.

There was also a paucity of outcomes identified as important to parents, who have a central role in monitoring and managing the health and treatment of their child with CKD. Physical, cognitive, and social-emotional development have been identified as a major parental concern.(56, 61) Linear growth (height and pubertal development and weight/BMI/body composition) were both reported in more than 25% of trials. However, no trials reported on neurocognitive development. Furthermore, parents share their children's concerns regarding school performance, social participation and mortality, all of which were underreported.(56, 61) We acknowledge that mortality rates are low in the pediatric population. However, the omission of outcomes that are of explicit importance to children and parents can diminish the relevance of trials.

Some outcomes were specific to certain stages of treatment. For example, graft function, graft loss, chronic graft rejection, graft histology/pathology, malignancy were specific to transplantation, while dialysis adequacy and vascular access complications were specific to dialysis. Many outcomes identified as clinically relevant to children undergoing dialysis or with a kidney transplant were also absent in most trials. In the 55 dialysis-specific trials, four of the five most commonly reported outcomes were surrogate markers (phosphate (21 [38.2%] dialysis specific trials), parathyroid hormone (18 [32.7%]), calcium (18 [32.7%]), bone density/markers (17 [31.0%]), and one was clinical (infection (17 [31.0%]). However, the primary concerns of children undergoing dialysis have been identified to be related to social participation, fatigue, school performance and exercise capacity and height.(60) Height/pubertal development was reported in only 7 (16%) dialysis-specific trials, and school performance and exercise capacity were reported in only one. Social participation and fatigue were not reported at all in dialysis-specific trials.

Among the 41 transplant-specific trials, the five most commonly reported outcomes were all surrogate outcomes: graft function (30 [73.2%] transplant-specific trials), acute graft rejection (20 [48.8%]), graft loss (19 [46.3%]), height and pubertal development (18 [44.0%]) and blood pressure (17 [41.5%]). Graft survival and physical side effects (e.g. changes in appearance) have been identified by pediatric kidney transplant recipients as important.(62) However, mortality was reported in only 14 [38%] transplant-specific studies, and physical side-effects and symptoms including weight gain (11 [30%]), pain (4 [10.8%]), and hyperhydrosis (1 [0.5%]) were rarely reported.

We have also demonstrated substantial multiplicity and inconsistency in outcome domains and measures across trials in children with CKD, with 6158 outcome measures and time points reported across the 100 outcome domains. Blood pressure (the most frequently reported outcome) was measured in 37% of trials, however had 56 different outcome measures. Without consistency

in the way outcomes are measured and reported, it is difficult to assess the relative effect of interventions across studies.(63) Furthermore, the majority of trials had a duration less than 24 months (63.4%) and a small sample size of 1-50 patients (62%), leading to considerable imprecision regarding treatment effects and uncertainty on the long-term impact of any treatment decisions.

A number of other studies have systematically evaluated the reporting of outcome domains in trials of pediatric conditions such as asthma,(56) autism,(64) appendicitis,(65) acute diarrheal illness,(26) neurodisability,(66) cerebral palsy(67) and otitis media.(68) These reviews have identified similar problems in outcome reporting. There is a dominance of clinical and physiological markers of short-term disease activity, and in contrast limited focus of QOL, functional status and long-term outcomes. Previous studies have also demonstrated a marked inconsistency across trials in the way that outcomes are measured and reported, non-uniformity in the definitions of clinical events used as endpoints, a lack of clarity in reporting methods, and problems with reporting bias.(24-26, 56, 64, 65)

This work provides a comprehensive and detailed analysis of the range and consistency of outcome domains and measures reported in trials in children across all stages of CKD. However, this review has some potential limitations. We used Cochrane reviews as a sampling frame as it was not feasible to include all trials, however the reviews cover the topics of importance in the field. We did not appraise the risk of bias in the included trials given our focus on the reporting of outcomes – not the results. Non-English trials were excluded and most studies were conducted in high-income countries.

Our findings emphasize the importance of developing a minimum set of core outcomes to be measured and reported in RCTs. Core outcome sets increase the likelihood that important outcomes will be measured, improve evidence synthesis by reducing heterogeneity between

studies, and reduce outcome reporting bias.(56) Core outcome sets have been developed for other medical conditions and the Core Outcome Measures in Effectiveness Trials (COMET) database(69) contains over 120 studies on the development of core outcome sets. However, studies in the pediatric setting are scarce although work has been done in the areas of otitis media,(61, 68) asthma,(56) neurodisability,(66) autism,(64) and cerebral palsy.(67) No core outcome set exists in pediatric CKD.

The Standardized Outcomes in Nephrology (SONG) Initiative, which commenced in 2014, aims to established a core outcome set across the spectrum of CKD that is based on the shared priorities of all stakeholders.(70) SONG-Kids is now underway, engaging children, parents and health professionals in a process to develop a core outcome set for trials in children and adolescents across all stages of CKD.(71)

There is a clear dominance of surrogate outcomes reported in trials in children with CKD, whilst outcomes that have direct relevance for children, their parents and clinicians are relatively rare. Furthermore, the heterogeneity and inconsistency in the way outcomes are defined, assessed and measured also limits ability to synthesize results across studies, including those assessing similar interventions. This reiterates an urgent need to improve the relevance and reliability of trials in decision making through the development of a core outcomes set to be reported as a minimum in trials in children with CKD. A core outcome set can be expected to improve outcome reporting in trials and subsequently lead to enhanced QOL, treatment satisfaction, and health outcomes of children and adolescents with CKD.

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List of abbreviations

Chronic kidney disease (CKD)

Randomized controlled trial (RCT)

Quality of life (QOL)

Figure legends

Figure 1; online. Search results

Figure 2. Number of trials reporting each outcome domain (total 205 trials, 100 outcome domains)

Figure 3. Number of outcomes measures (definitions and time points) for the most frequently reported and pediatric-specific outcome domains among trials

Figure 4a; online. Frequency of outcomes measures (definitions and time points) among trials reporting blood pressure (76 trials, 56 outcomes measures)

Figure 4b; online. Frequency of outcomes measures (definitions and time points) among trials reporting relapse/remission (67 trials, 82 outcomes measures)

Figure 4c; online. Frequency of outcomes measures (definitions and time points) among trials reporting kidney function (66 trials, 47 outcomes measures)

Figure 4d; online. Frequency of outcomes measures (definitions and time points) among trials reporting infection (61 trials, 114 outcomes measures)

Figure 4e; online. Frequency of outcomes measures (definitions and time points) among trials reporting height and pubertal development (52 trials, 34 outcomes measures

Figure 4f; online. Frequency of outcomes measures (definitions and time points) among trials reporting dermatologic disorder (46 trials, 24 outcomes measures)

Figure 4g; online. Frequency of outcomes measures (definitions and time points) among trials reporting pain (34 trials, 27 outcomes measures)

Figure 4h; online. Frequency of outcomes measures (definitions and time points) among trials reporting psychological impact (15 trials, 10 outcomes measures)

Figure 4i; online. Frequency of outcomes measures (definitions and time points) among trials reporting weight/BMI/body composition (50 trials, 40 outcomes measures)

Table 1. Characteristics of included trials (n=205)

Trial characteristic	Number of trials (%)
Year of publication	
<1980	13 (6.3)
1980-1989	18 (8.8)
1990-1999	54 (26.3)
2000-2009	77 (37.6)
≥2010	43 (21.0)
Duration of trial (months)	
< 3	24(11.7)
3 – 5	26(12.7)
6 – 11	32 (15.6)
12 – 23	48(23.4)
≥ 24	75(36.6)
Sample size (n)	
1 to 50	127 (62.0)
51 to 100	39 (19.0)
101 to 150	19 (9.3)
151 to 200	11 (5.3)
>200	6 (2.9)
Unspecified	3 (1.5)
Location	
America	66 (32.2)
Europe	53 (25.9)
Asia	51 (24.9)
Africa	6 (2.9)
Oceania	1 (0.5)
Multinational studies	28 (13.7)
CKD stage *	

1 to 5	123 (52.1)
Hemodialysis	32 (13.6)
Peritoneal dialysis	40 (16.9)
Kidney transplantation	41 (17.4)
Primary kidney disease	
Nephrotic syndrome	31 (10.3)
Congenital abnormalities of the kidney and urinary tract (CAKUT)	25 (8.3)
Focal segmental glomerulosclerosis (FSGS)	24 (8.0)
Obstructive uropathy	14 (4.7)
Hemolytic uraemic syndrome (HUS)	13 (4.3)
Glomerulonephritis	12 (4.0)
Other	121 (40.2)
Non-specified	61 (20.3)
Intervention type	
Immunomodulation	100 (48.8)
Bone health	40 (19.5)
Dietary/nutritional	15 (7.3)
Hematological	11 (6.0)
Anti-hypertensive agent	8 (3.9)
Lipid lowering agents	7 (3.4)
Dialysis-specific	6 (2.9)
Anti-infective agents	5 (2.4)
Diuretics	1 (0.5)
Other	12 (5.9)

***** Multiple categories possible

Table 2; online only. Proportion of trials reporting each surrogate outcome (205 trials, 51 outcome domains)

Domains (surrogate outcomes)	Number of trials		
	All n=205 (%)	Dialysis n=55 (%)	Transplantation n=41 (%)
Blood pressure	76 (37.1)	14 (25.5)	17 (41.5)
Relapse/remission	70 (34.1)	1 (1.8)	1 (2.4)
Kidney function	66 (32.2)	5 (9.1)	3 (7.3)
Weight/BMI/body composition	50 (24.4)	7 (12.7)	12 (29.3)
Proteinuria, albuminuria	49 (23.9)	2 (3.6)	3 (7.3)
Blood protein, albumin	48 (23.4)	9 (16.4)	3 (7.3)
Lipids	47 (22.9)	6 (10.9)	16 (39.0)
Anemia/haemoglobin/iron	44 (21.5)	15 (27.3)	8 (20.0)
Phosphate	39 (19.0)	21 (38.2)	7 (17.1)
White blood cells	39 (19.0)	1 (1.8)	8 (19.5)
Bone density/markers	37 (18.0)	17 (30.9)	7 (17.1)
Calcium	34 (16.6)	18 (32.7)	6 (14.6)
Urea	31 (15.1)	8 (14.5)	4 (9.8)
Glucose metabolism	31 (15.1)	9 (16.4)	16 (39.0)
Parathyroid hormone	31 (15.1)	18 (32.7)	6 (14.6)
Graft function	30 (14.6)		30 (73.2)
Electrolytes (other)	25 (12.2)	5 (9.1)	8 (19.5)
Liver function	24 (11.7)	3 (5.5)	4 (9.8)
Potassium	22 (10.7)	6 (10.9)	4 (9.8)
Acute graft rejection	20 (9.8)	2 (3.6)	20 (48.8)
Inflammatory markers/oxidative stress	19 (9.3)	6 (10.9)	6 (14.6)
Acid-base balance	25 (12.2)	11 (20.0)	4 (9.8)
Vitamin D	15 (7.3)	9 (16.4)	2 (4.9)
Dialysis adequacy	13 (6.3)	13 (23.6)	-
Platelets, coagulation	14 (6.8)	3 (5.5)	2 (4.9)
Kidney disease progression/change	12 (5.9)	1 (1.8)	1 (2.4)
Graft rejection (unspecified)	11 (5.4)	-	11 (26.8)

Growth hormone	11 (5.4)	5 (9.1)	5 (12.2)
Respiratory function	11 (5.4)	3 (5.5)	4 (9.8)
Acute kidney injury	9 (4.4)	-	1 (2.4)
Serum immunoglobulins	9 (4.4)	1 (1.8)	1 (2.4)
Calcium x Phosphate	9 (4.4)	6 (10.9)	-
Graft histology/ pathology (excl. rejection)	8 (3.9)	-	8 (19.5)
Uric acid	8 (3.9)	1 (1.8)	-
Caloric intake	8 (3.9)	4 (7.3)	-
Protein intake	7 (3.4)	3 (5.5)	-
Electrolyte intake	7 (3.4)	5 (9.1)	-
Renal tubular dysfunction	6 (2.9)	3 (5.5)	-
Fertility	5 (2.4)	2 (3.6)	-
Cardiac function	5 (2.4)	1 (1.8)	-
Rhabdomyolysis	5 (2.4)	1 (1.8)	2 (4.9)
Endocrine function	4 (2.0)	1 (1.8)	1 (2.4)
Nitrates	3 (1.5)	1 (1.8)	1 (2.4)
Thyroid function	3 (1.5)	1 (1.8)	1 (2.4)
Amino acids	3 (1.5)	2 (3.6)	-
Aluminium toxicity	2 (1.0)	1 (1.8)	-
Urine volume	2 (1.0)	1 (1.8)	-
Blood pressure regulating hormone	2 (1.0)	-	-
Carnitine	2 (1.0)	2 (3.6)	-
Chronic graft rejection	2 (1.0)	-	2 (4.9)
Vitamin E	1 (0.5)	-	-
Donor-specific anti-HLA antibody	1 (0.5)	-	1 (2.4)

-, no trials reported

Table 3; online only. Proportion of trials reporting each clinical outcome (205 trials, 38 outcome domains)

Domains (clinical outcomes)	Number of trials		
	All n=205 (%)	Dialysis n=55 (%)	Transplantation n=41 (%)
Infection	61 (29.8)	17 (30.9)	16 (39.0)
Height and pubertal development	51 (24.9)	12 (21.8)	18 (43.9)
Dermatologic disorder	46 (22.4)	5 (9.1)	4 (9.8)
Gastrointestinal effects	43 (21.0)	7 (12.7)	8 (19.5)
Adverse events (non-specified)	36 (17.6)	6 (10.9)	10 (24.4)
Mortality	28 (13.7)	3 (5.5)	15 (36.6)
Neurologic disorders	26 (12.7)	3 (5.5)	6 (14.6)
Urologic complication	23 (11.2)	2 (3.6)	6 (14.6)
Respiratory disease	22 (10.7)	4 (7.3)	6 (14.6)
Graft loss	19 (9.3)	-	19 (46.3)
Vision disorder	18 (8.8)	2 (3.6)	1 (2.4)
Mouth and gum disorders	14 (6.8)	-	3 (7.3)
Bone disease/fractures	14 (6.8)	4 (7.3)	5 (12.2)
Cushing syndrome	14 (6.8)	-	1 (2.4)
Cardiovascular disease	8 (3.9)	4 (7.3)	1 (2.4)
Dialysis treatment complications	8 (3.9)	7 (12.7)	2 (4.9)
Malignancy – PTLD	8 (3.9)	-	8 (19.5)
Malignancy (unspecified)	6 (2.9)	1 (1.8)	3 (7.3)
Edema	6 (2.9)	2 (3.6)	-
Hospitalization	6 (2.9)	1 (1.8)	4 (9.8)
Procedural complication	5 (2.4)	-	1 (2.4)
Allergic reaction	5 (2.4)	3 (5.5)	-
Bleeding/hematoma	5 (2.4)	1 (1.8)	1 (24)
Muscular complications	5 (2.4)	1 (1.8)	3 (7.3)
Requirement of transplantation	4 (2.0)	2 (3.6)	-
Fever/chills	4 (2.0)	2 (3.6)	2 (4.9)
Compliance	4 (2.0)	3 (5.5)	1 (2.4)

Time on dialysis	3 (1.5)	1 (1.8)	2 (4.9)
Metabolic and nutritional disorders	3 (1.5)	-	1 (2.4)
End stage kidney disease	3 (1.5)	-	-
Dehydration	2 (1.0)	-	2 (4.9)
Arthritis and joint pain	2 (1.0)	-	-
Hearing impairment	2 (1.0)	1 (1.8)	-
Physical injury	2 (1.0)	1 (1.8)	-
Vascular access complications	1 (0.5)	1 (1.8)	-
Malignancy - skin	1 (0.5)	-	1 (2.4)
Pulmonary embolus	1 (0.5)	-	-
Hyperhidrosis	1 (0.5)	-	-

Table 4; online only. Proportion of trials reporting each patient-reported outcome (205 trials, 10 outcome domains)

Domains (patient-reported outcomes)	Number of trials		
	Total trials, n=205 (%)	Dialysis trials, n=55 (%)	Transplantation trials, n=41 (%)
Pain	33 (16.1)	12 (21.8)	5 (12.2)
Psychological impact	15 (7.3)	1 (1.8)	-
Treatment satisfaction	2 (1.0)	1 (1.8)	1 (2.4)
Sleep disorder	2 (1.0)	1 (1.8)	-
Fatigue	2 (1.0)	-	-
Quality of life (global)	2 (1.0)	1 (1.8)	-
Depression	2 (1.0)	1 (1.8)	-
Food enjoyment/appetite	2 (1.0)	1 (1.8)	-
School performance	1 (0.5)	1 (1.8)	-
Physical function/mobility/ disability	1 (0.5)	1 (1.8)	-

Table 5. Proportion of trials reporting the top 10 most frequently reported outcome domains

Domains (all outcomes)	Number of trials		
	All n=205 (%)	Dialysis n=55 (%)	Transplantation n=41 (%)
Blood pressure	76 (37.1)	14 (25.5)	17 (41.5)
Relapse/remission	70 (34.1)	1 (1.8)	1 (2.4)
Kidney function	66 (32.2)	5 (9.1)	3 (7.3)
Infection	61 (29.8)	17 (30.9)	16 (39.0)
Height and pubertal development	51 (24.9)	12 (21.8)	18 (43.9)
Weight/BMI/body composition	50 (24.4)	7 (12.7)	12 (29.3)
Proteinuria, albuminuria	49 (23.9)	2 (3.6)	3 (7.3)
Blood protein, albumin	48 (23.4)	9 (16.4)	3 (7.3)
Lipids	47 (22.9)	6 (10.9)	16 (39.0)
Dermatologic disorder	46 (22.4)	5 (9.1)	4 (9.8)

Table 6; online only. Primary outcomes reported in trials conducted in children with CKD

Domains of primary outcomes (96 trials*)	Number of trials (%)
Relapse/remission	43 (44.8)
Proteinuria, albuminuria	22 (22.9)
Kidney function	18 (18.8)
Height and pubertal development	15 (15.6)
Anemia/haemoglobin/iron	9 (9.4)
Bone density/markers	6 (6.3)
Acute graft rejection	5 (5.2)
Adverse events	5 (5.2)
Glucose metabolism	5 (5.2)
Infection	5 (5.2)
Lipids	5 (5.2)
Parathyroid hormone	4 (4.2)
Pain	3 (3.1)
Kidney disease progression/change	3 (3.1)
Dialysis adequacy	3 (3.1)
Cardiac function	2 (2.1)
Cushing's syndrome	2 (2.1)
Urologic complication	2 (2.1)
Phosphate	2 (2.1)
Graft rejection (unspecified)	2 (2.1)
Other	14 (14.6)

* 96 out of 205 trials reported primary outcomes

Figure 1; online only

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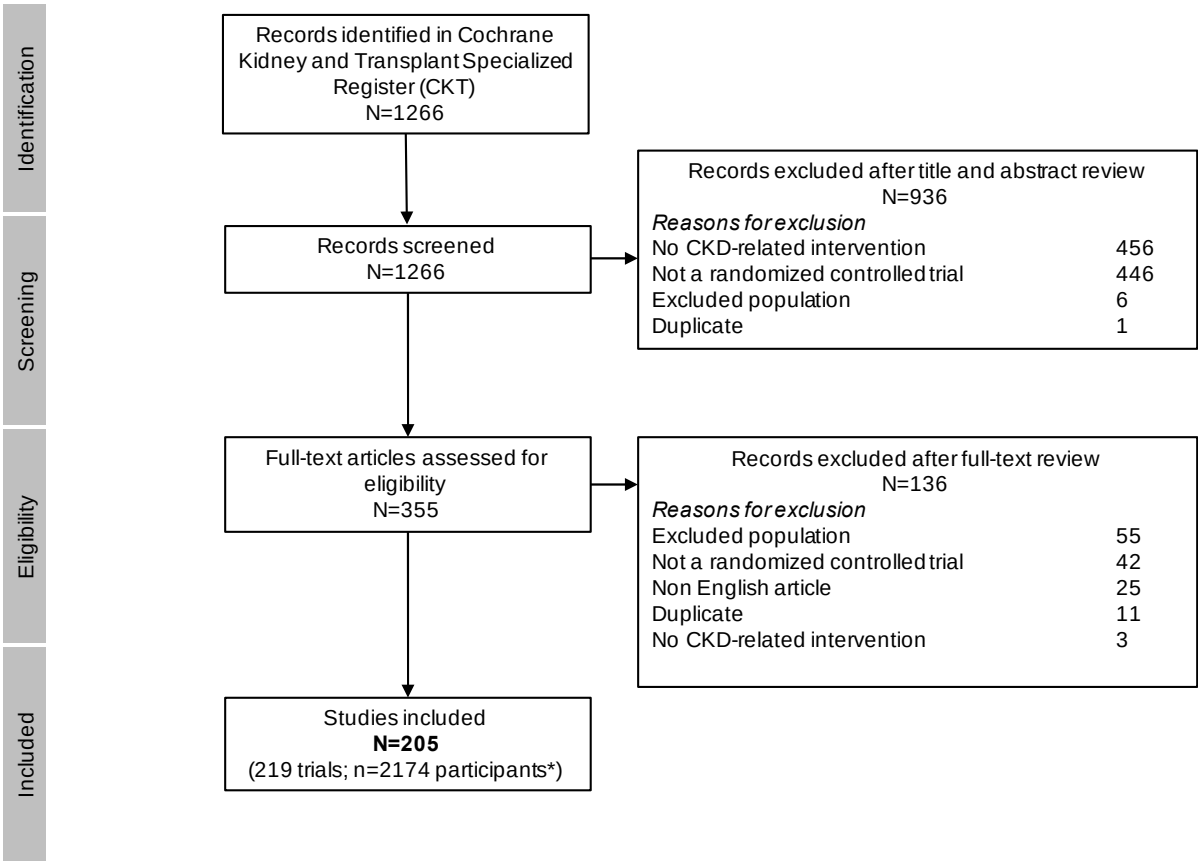

*Sample size not included in 3 studies

Figure 2

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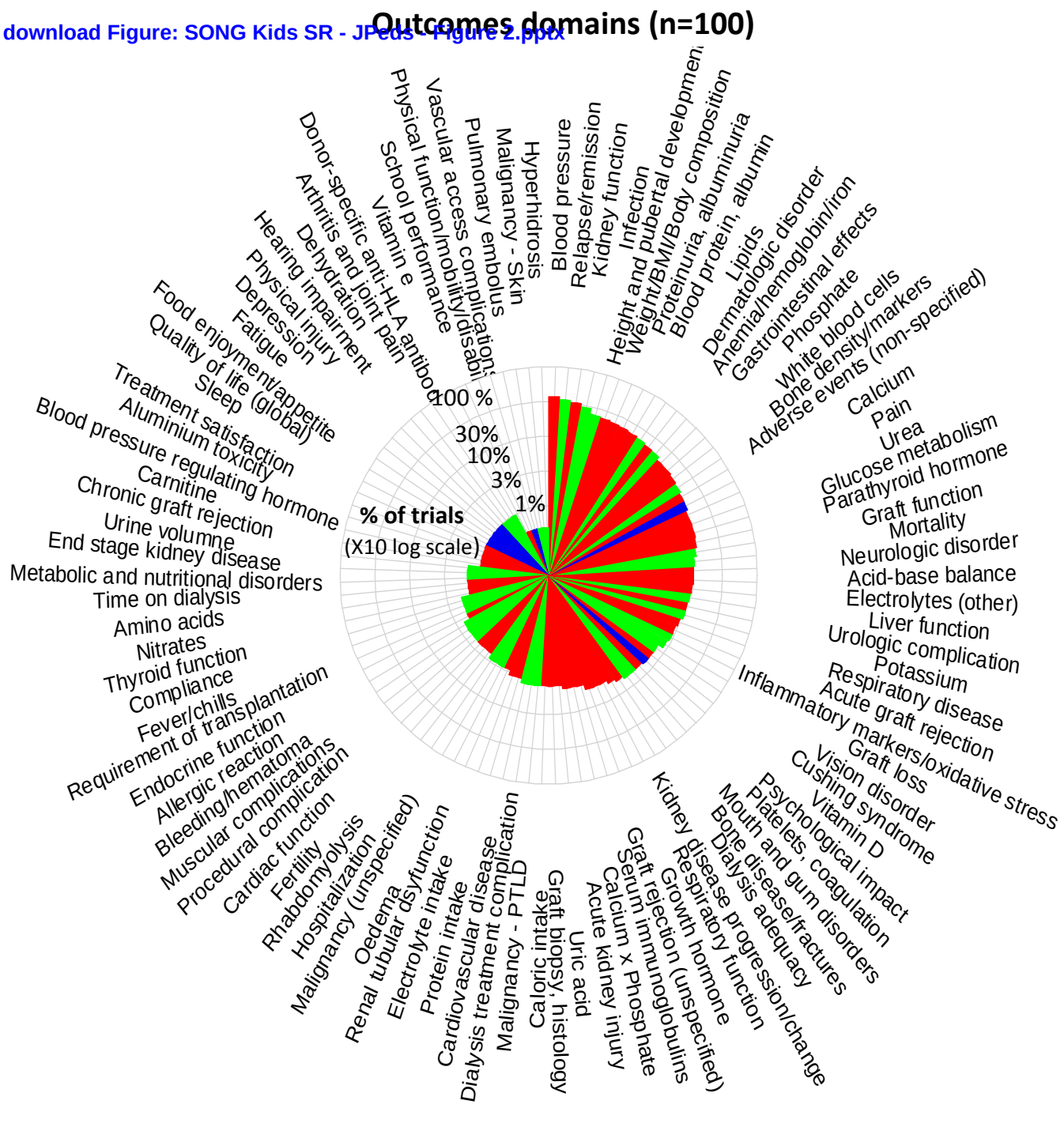

Categories of outcome:

- Surrogate (n=52)
- Clinical (n=38)
- Patient reported, (n=10)

NB: Proportion are expressed in a x10 log scale to display proportion <1%

Figure 3

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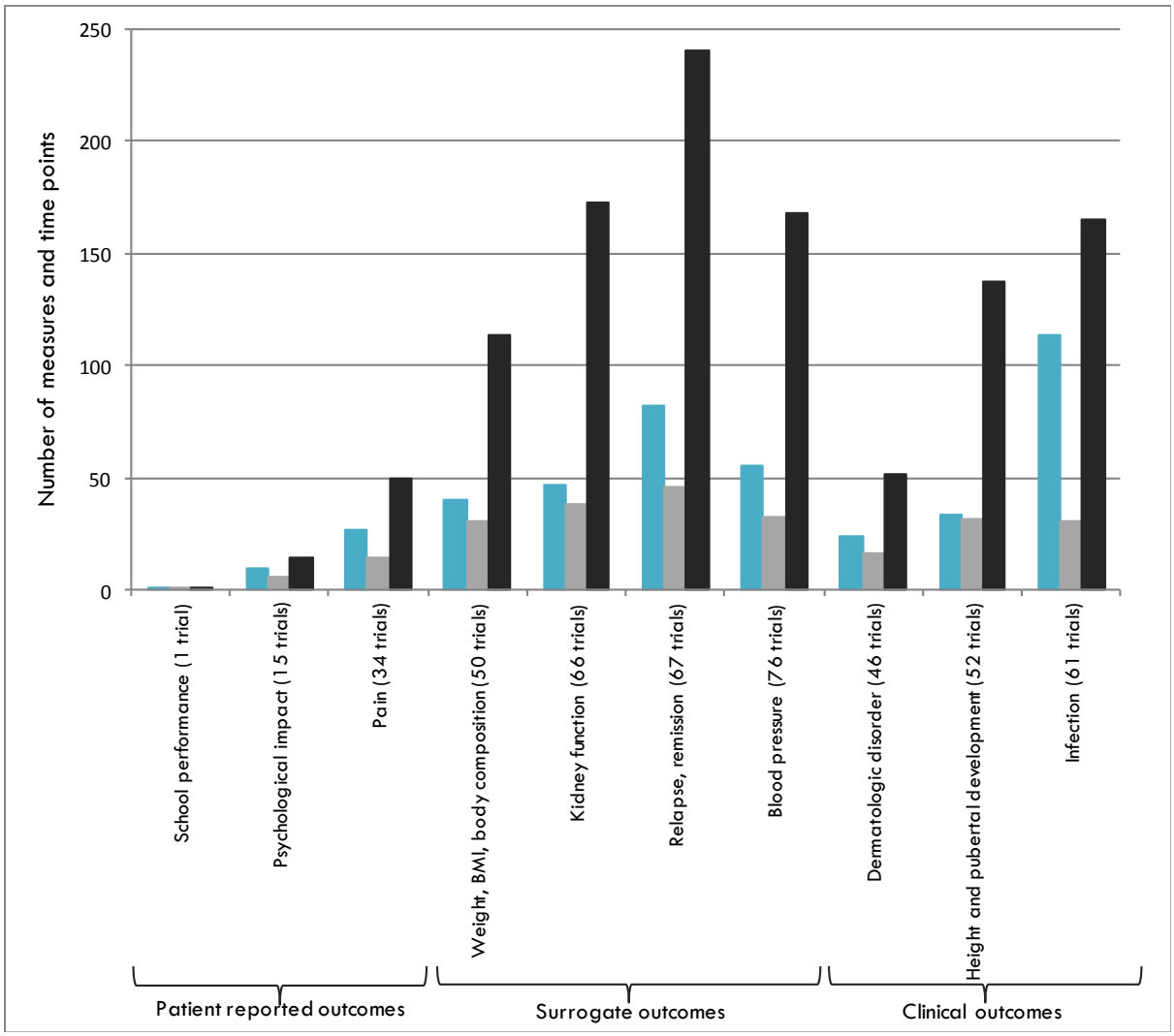

Figure Legend

 Number of measures

 Number of time points *

 Number of measures and time points **

*Number of unique time points
**Different measures can have the same time points

Figure 4a; online only

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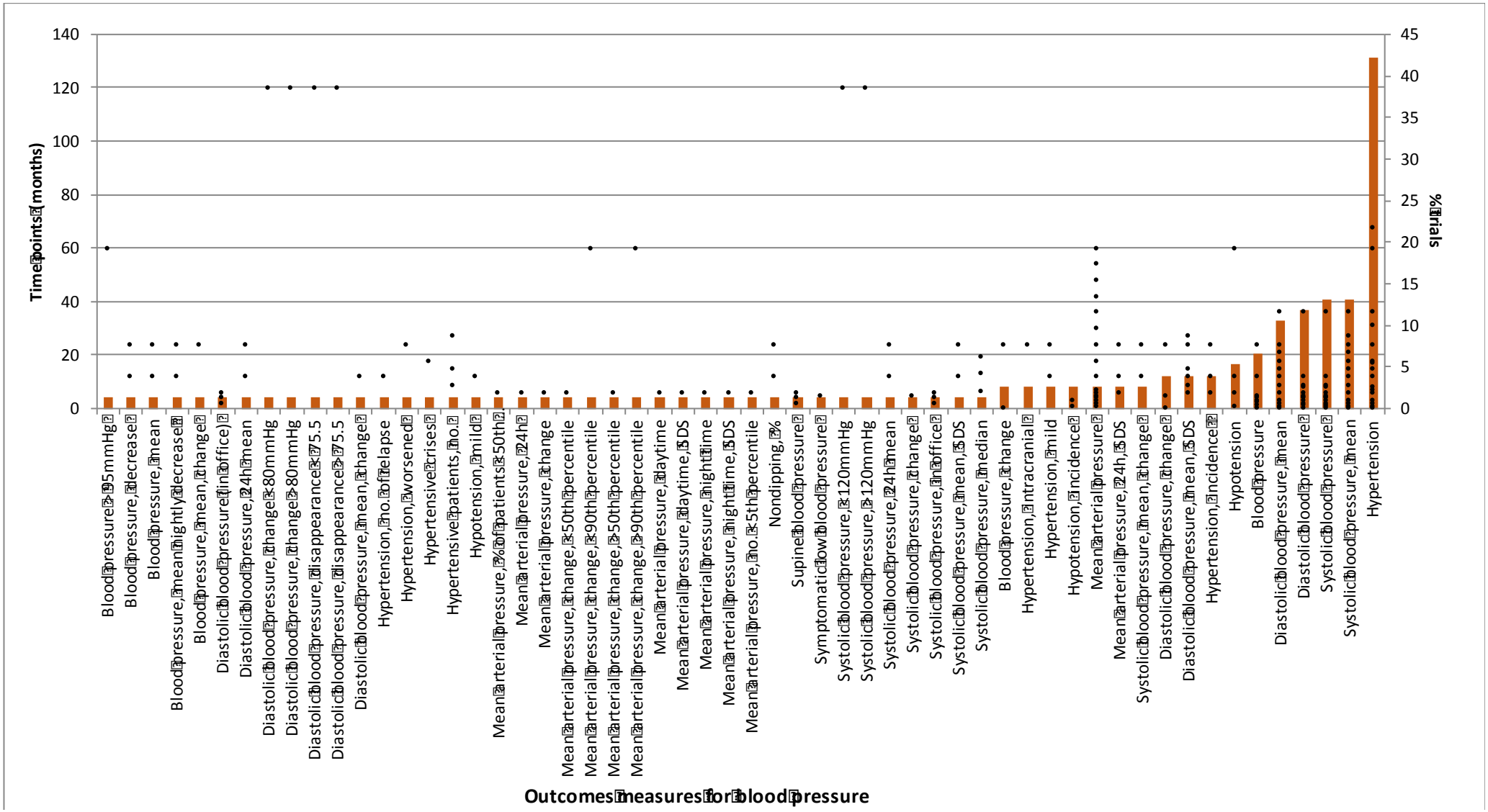

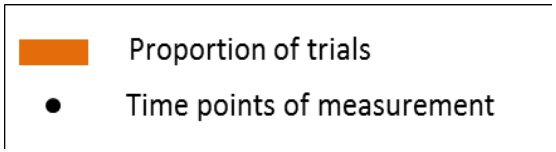

* Outcome measures shown are as named in the trials

Figure 4b; online only

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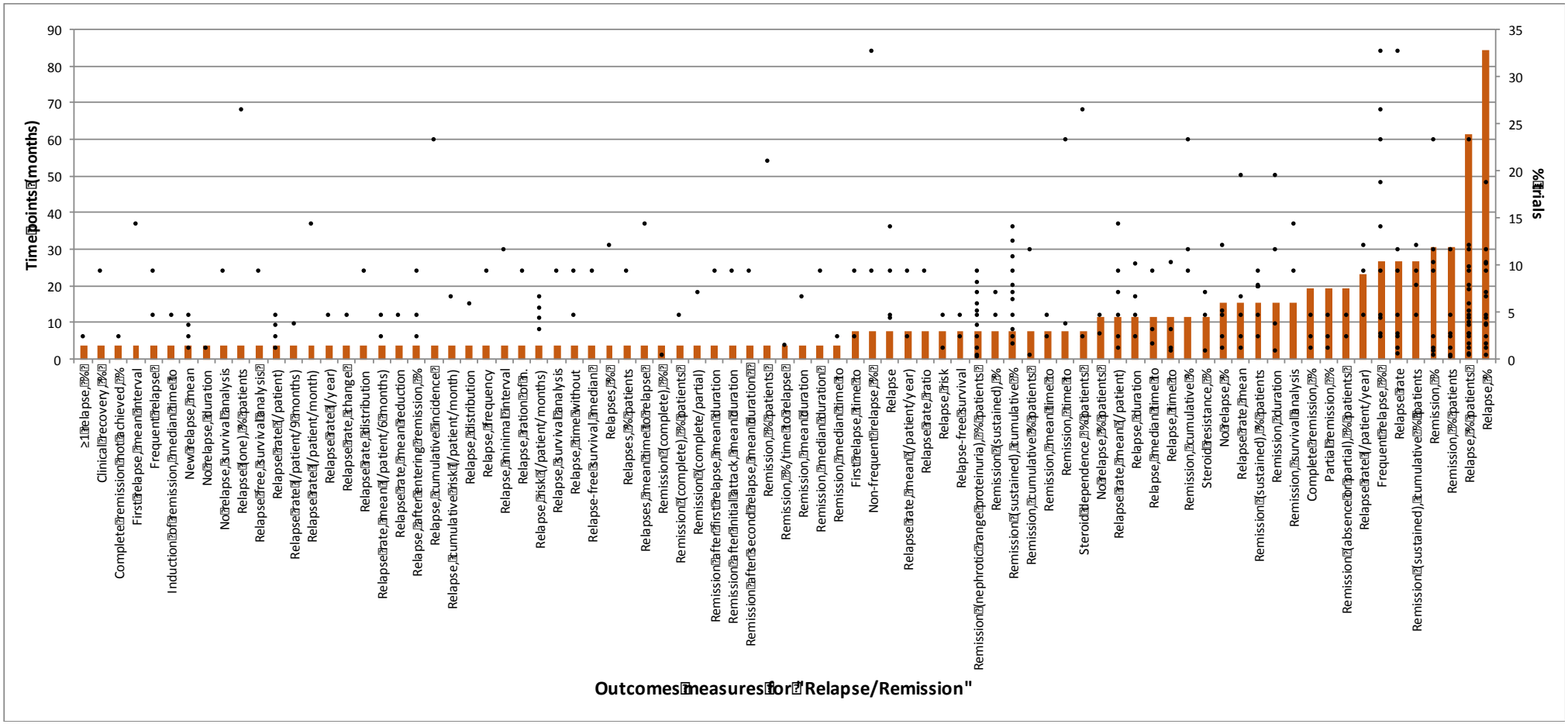

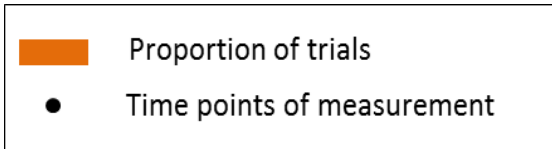

* Outcome measures shown are as named in the trials

Figure 4c; online only

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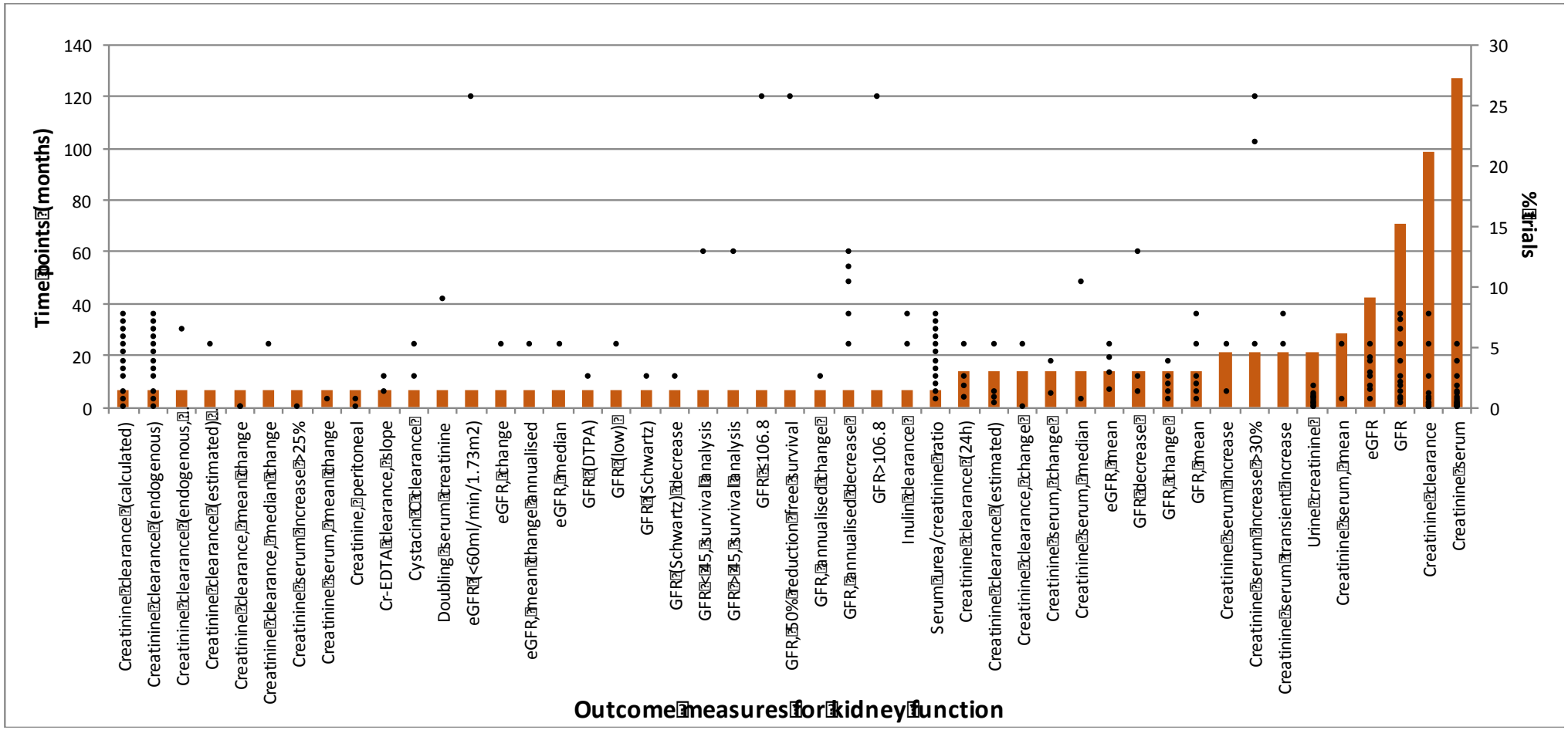

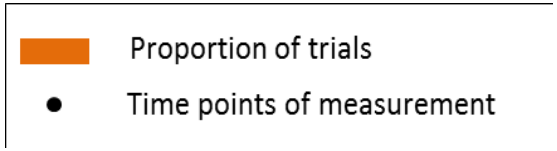

* Outcome measures shown are as named in the trials

Figure 4d; online only

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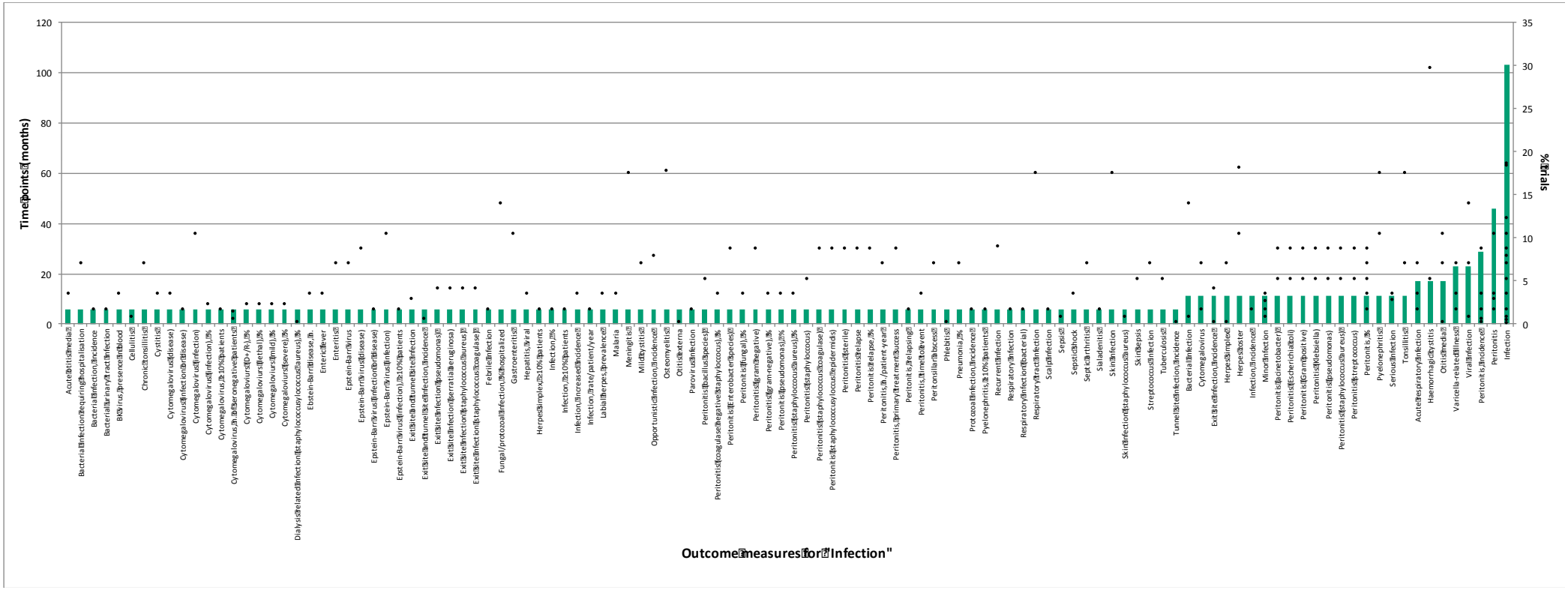

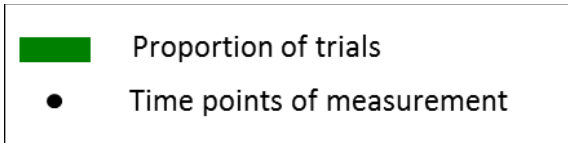

* Outcome measures shown are as named in the trials

Figure 4e; online only

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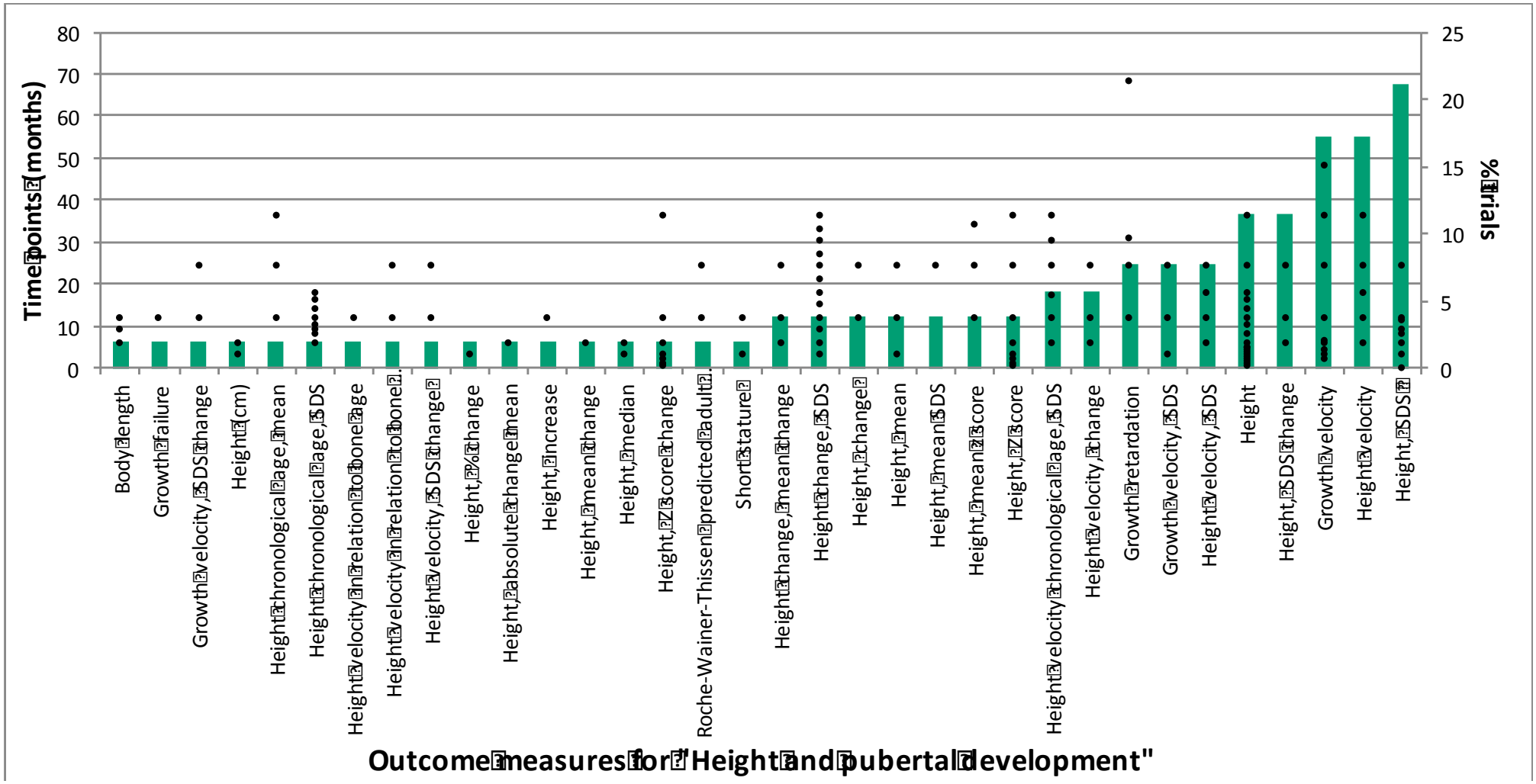

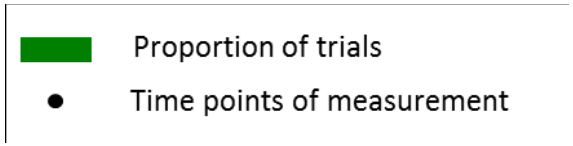

* Outcome measures shown are as named in the trials

Figure 4f; online only

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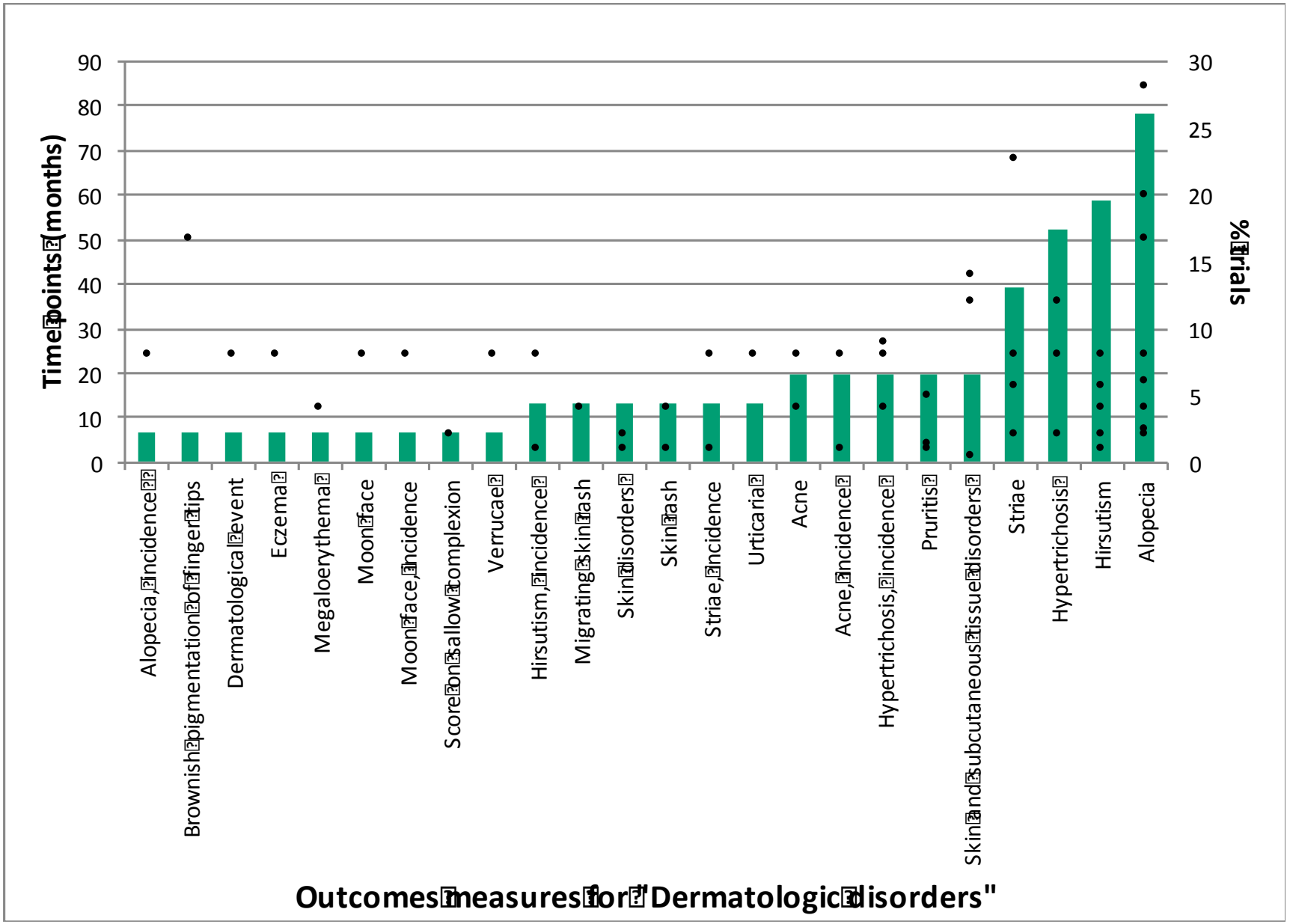

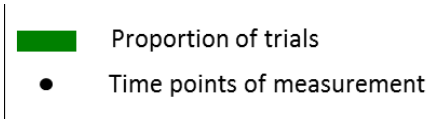

* Outcome measures shown are as named in the trials

Figure 4g; online only

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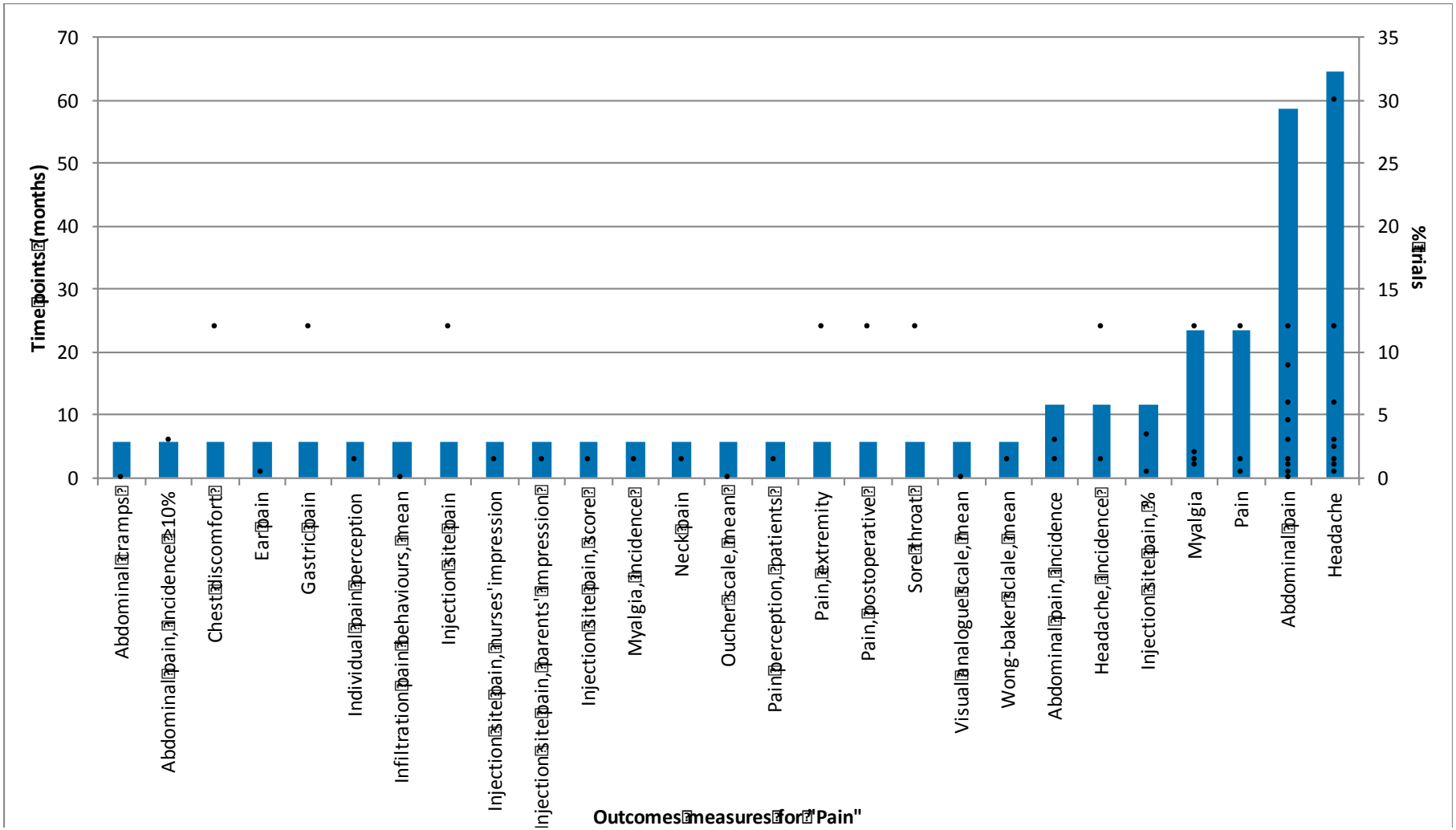

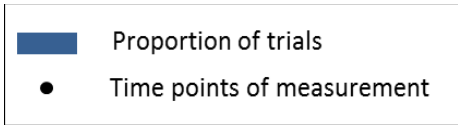

* Outcome measures shown are as named in the trials

Figure 4h; online only

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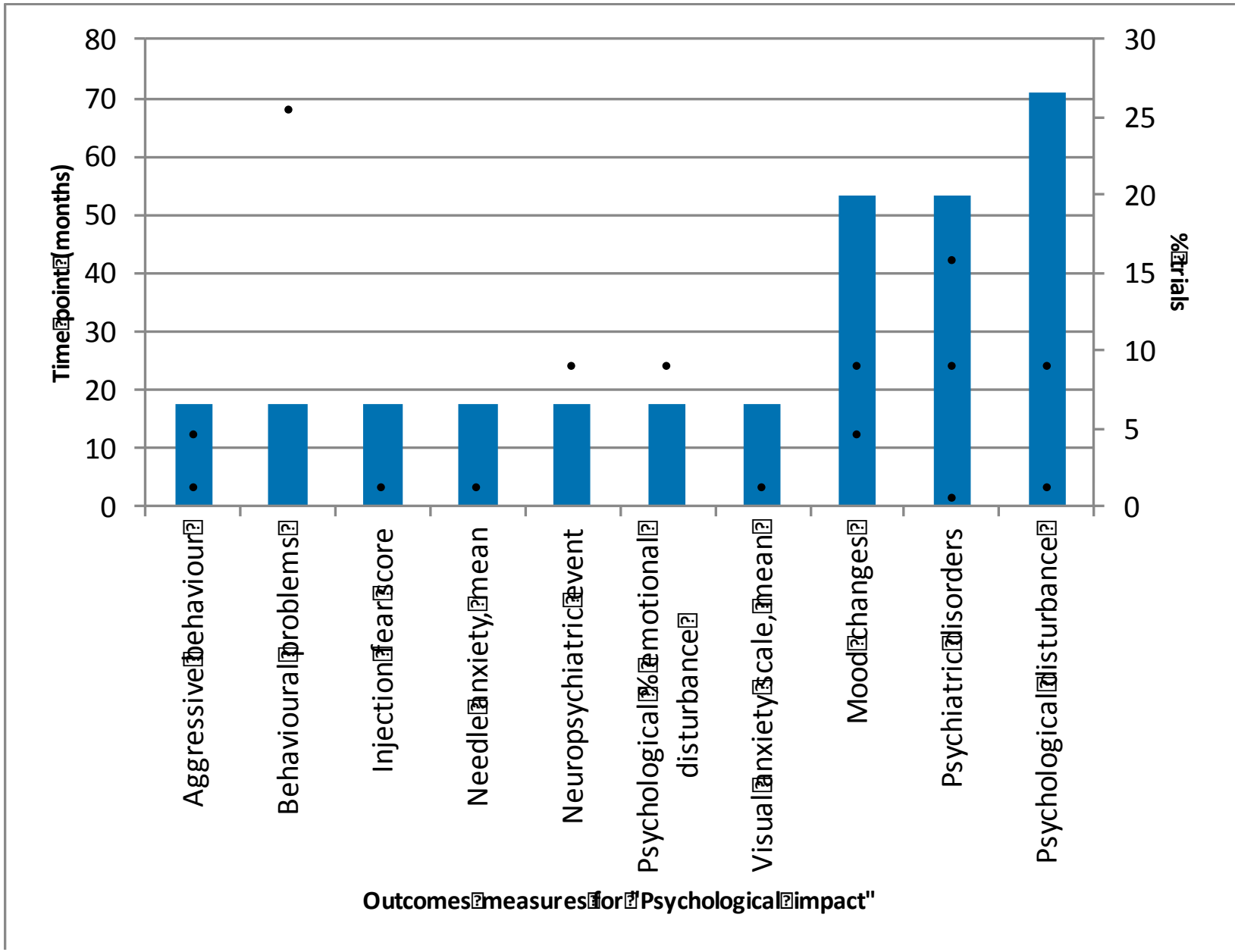

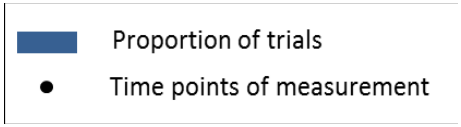

* Outcome measures shown are as named in the trials

Figure 4i; online only

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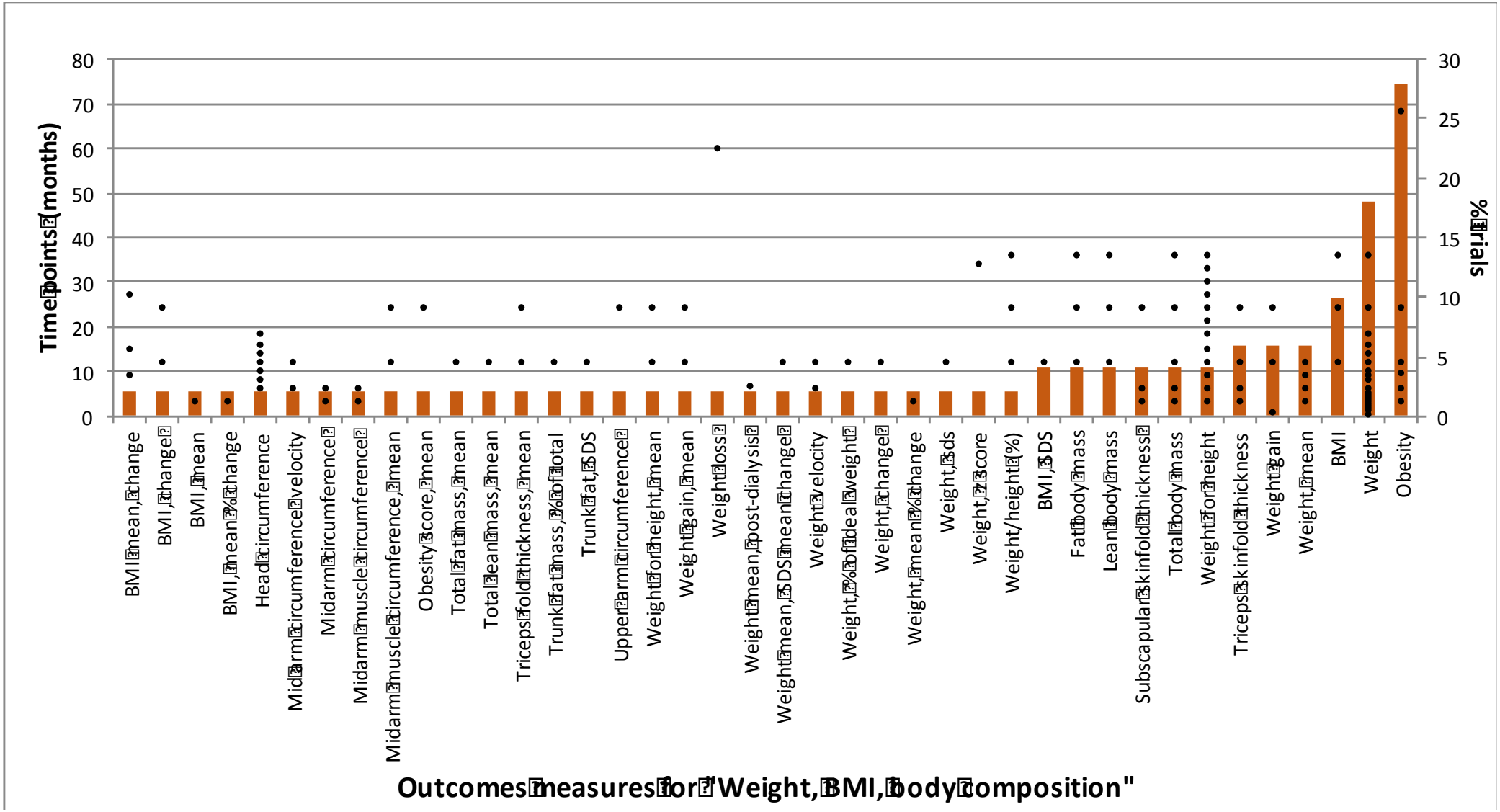

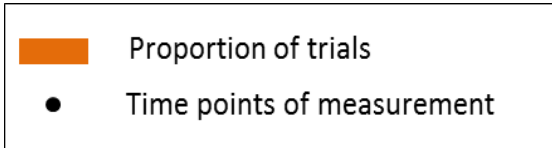

* Outcome measures shown are as named in the trials