15 years of patient-reported outcomes in clinical trials leading to GU cancer drug approvals: a systematic review on the quality of data reporting and analysis

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Summary

Background Standardized, high-quality PRO data reporting is crucial for patient centered care in the field of oncology, especially in clinical trials that establish standard of care. This study evaluated PRO endpoint design, conduct and reporting methods in FDA approved drugs for GU malignancies.

Methods A systematic review of the FDA archives identified GU cancer drug approvals from Feb 2007 to July 2022. ClinicalTrials.gov and PubMed were used to retrieve relevant data. PRO data was screened, and analytic tools, interpretation methods in the published papers and study protocols were reviewed. Compliance with PRO reporting standards were assessed using PRO Endpoint Analysis Score (PROEAS), a 24-point scoring scale from Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium (SISAQOL).

Findings We assessed 40 trial protocols with 27,011 participants, resulting in 14 renal cell cancer (RCC), 16 prostate cancer (PC), and 10 urothelial cancer (UC) approvals. PRO data was published for 27 trials, with 23 PRO publications (85%) focusing solely on PRO data, while 4 (15%) included PRO data in the original paper. Median time between primary clinical and secondary paper with PRO data was 10.5 months (range: 9–25 months). PROs were not planned as primary endpoints for any study but 14 (52%) reported them as secondary, 10 (37%) as exploratory outcomes, and 3 (11%) lacked any clarity on PRO data as endpoint. Mean PROEAS score of all GU cancers was 11.10 (range: 6–15), RCC (11.86, range: 6–15), UC (11.50, range: 9–14), and PC (10.56, range: 6–15). None met all the SISAQOL recommendations.

Interpretation Low overall PROEAS score and delays in PRO data publication in GU cancer drug trials conducted in the past decade emphasize the need for improvement in quality of design and conduct of PRO endpoint in future trials and accelerated publication of PRO endpoints, using standardized analysis, and prespecified hypothesis driven endpoint. These improvements are essential for facilitating interpretation and application of PRO study findings to define patient care.

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Keywords: Patient reported outcomes; Renal cell cancer; Prostate cancer; Urothelial cancer

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Research in context

Evidence before this study

Patient reported outcomes (PROs) promote patient-centeredness in clinical trials; the US Food and Drug Administration (FDA) encourages PRO analyses in drug development and approval. Current evidence on the standardization and quality in PRO conduct and reporting for clinical trials that lead to the FDA approval of drugs in genitourinary (GU) cancers is lacking. We conducted a systematic review of the FDA archives to identify GU cancer drugs approved between February 2007 and July 2022. For each GU drug approval, the pivotal clinical trial(s) were identified and retrieved from both PubMed and ClinicalTrials.gov. We assessed 40 clinical trial protocols with the aim to address gaps and provide a comprehensive assessment of PRO endpoint design, conduct and reporting in GU cancer drugs.

Added value of this study

This study contributes significantly to the existing body of evidence by conducting a systematic review and scoring analysis of the PRO reporting in FDA-approved GU cancer drugs. Unlike previous studies that focused on specific aspects of PRO reporting, this research provides a comprehensive evaluation of protocols, manuscripts, and publications related to clinical trials leading to GU cancers FDA drug approvals. This study also examines the timing of PRO data publication and explores the types of end points, PRO instruments used, and methods to address missing data.

Implications of all the available evidence

The study highlights specific opportunities for improvement in PRO endpoints design, conduct, data collection and analysis for future FDA-registrational cancer therapy studies. The delays in publishing PRO data and the limited use of standardized methods hinder the timely evaluation and utilization of these outcomes in clinical practice. This study aims to drive improvements in PRO endpoint trial design and data reporting practices in GU cancer drug development and ultimately enhance patient-centered cancer care.

Introduction

GU cancers are a diverse group of malignancies, accounting for more than 20% of cancer cases and deaths in the United States, with an estimated 444,660 new cases and 67,330 deaths in 2022.[1] While traditional chemotherapy was commonly used in the past, advancements in drug development in the last 15 years have led to the approval of multiple systemic therapies by the FDA.[2–6] Numerous clinical trials are exploring novel immune based therapies, targeted therapies, antibody–drug conjugates (ADC), theranostic therapies and combinations of all these novel types of therapies for prostate cancer, renal cell carcinoma, and urothelial carcinoma.[7] Patient reported outcomes (PROs) have gained attention as valuable data in clinical trials,[8–10] allowing for the assessment of treatment benefits and risks from the patient's perspective, including quality of life and symptom evaluation.[11–13] The incorporation of PRO endpoints in trial design facilitates patient-centered drug development and care, prioritizing factors such as safety, tolerability, and efficacy.[14–16]

However, there are challenges in PRO data synthesis, analysis, and reporting, with poorly defined objectives and inadequate reporting of results in many protocols and primary trial publications.[17–24] In a systemic review conducted between 2014 and 2018 in bladder cancer revealed statistical approaches for dealing with missing data were not reported in 75% of studies.[25] Different groups have reported on PRO data within multiple GU malignancies including a mini review by Decat Bergerot et al., 2020. These reviews have noted the growing recognition and enthusiasm of PRO in clinical trials, identifying issues with standardization of testing and testing timelines as legitimate challenges.[26–29]

Despite these limitations, PROs have the potential to serve as surrogate endpoints to measure outcomes and effects of the intervention on one or more pertinent clinical measures, including health-related quality of life (HRQoL) and symptoms, aiding in clinical decision-making and policy development.[30,31] Recommendations such as SPIRIT-PRO and CONSORT-PRO have been proposed to improve PRO reporting in protocols and publications, along with the development of best practices and data analysis guidelines by the SISAQOL consortium.[20,32,33] Our group previously developed a 24-point quantitative scoring scale to evaluate the quality of the methods used to report and analyze PROs in the randomized clinical trials (RCTs): PROEAS, based on the 2020 recommendations of the SISAQOL Consortium.[34] These initiatives will hopefully lead to much needed patient centered treatment recommendations and policy making, especially in an era with limited financial resources for health care.[35]

In this study we systematically reviewed the trial protocols, primary publications, and PRO publications of drugs from February 2007 to July 2022 that have been authorized by the FDA for utilization in GU cancers, to assess the current quality of PRO data collection, synthesis, analysis, and reporting. The goals of the study were to assess the standardization level over the past 15 years in protocol design, data collection, and reporting of PRO endpoints and data. This aimed to fill a gap in the current knowledge in GU caners and will allow for

understanding the areas of improvement in GU cancers trial development in respect to the quality and standardization of PRO trial endpoints design and conduct in future GU cancers study protocols.

Methods

Search strategy for studies selection

All FDA approved GU therapies were identified through an exhaustive systematic review of the FDA archives, covering cancer drug approvals from February 2007 to July 2022 (Annex). Four authors (M.T., H.S., J.S.C, J.J.A) identified 40 clinical trial protocols meeting the study criteria within the same timeframe, based on the inclusion only of clinical trials used for reporting the FDA approval. These therapies included targeted treatments, immunotherapies, monoclonal antibodies, anti-angiogenesis drugs, antibody–drug conjugates, theragnostic therapies and cytotoxic chemotherapies. Drug modifications were excluded from this study. For each GU drug approval, only the pivotal clinical trial(s) that were included for the FDA approval were identified and retrieved from both PubMed and ClinicalTrials.gov. We attempted to source each trial's protocol (final approved version), its primary publication reporting the clinical results, and any secondary publication reporting PROs. A primary publication was defined as the first or principal publication that included the primary outcome(s) of the clinical trial results, and a secondary publication was defined as one published following or in support of the primary article. When available, PROs from both published journal articles and study protocols were collected. An FDA approval was considered to include PRO data if they were reported in at least one of the supporting trials via a primary publication or in a separate PRO-specific publication. The methodology adhered to the guidelines detailed in the Cochrane Handbook for Systematic Reviews for identification of secondary PRO papers related to clinical trials leading to GU drug approvals.[36]

PubMed was used to identify supporting trial manuscripts for each FDA approval along with clinicaltrials.gov using the keywords: quality of life [MeSH Terms] OR quality of life [Text Word] OR patient reported outcomes [Text Word] AND drug approved name [All Fields]. Abstracts, publications of preliminary results, and interim analysis were excluded with the aim to limit the results to only high-level PRO results. Investigators extracted trial characteristics and determined the availability of PRO trial results. Fig. 1 shows the detailed inclusion and exclusion criteria used. Since this study

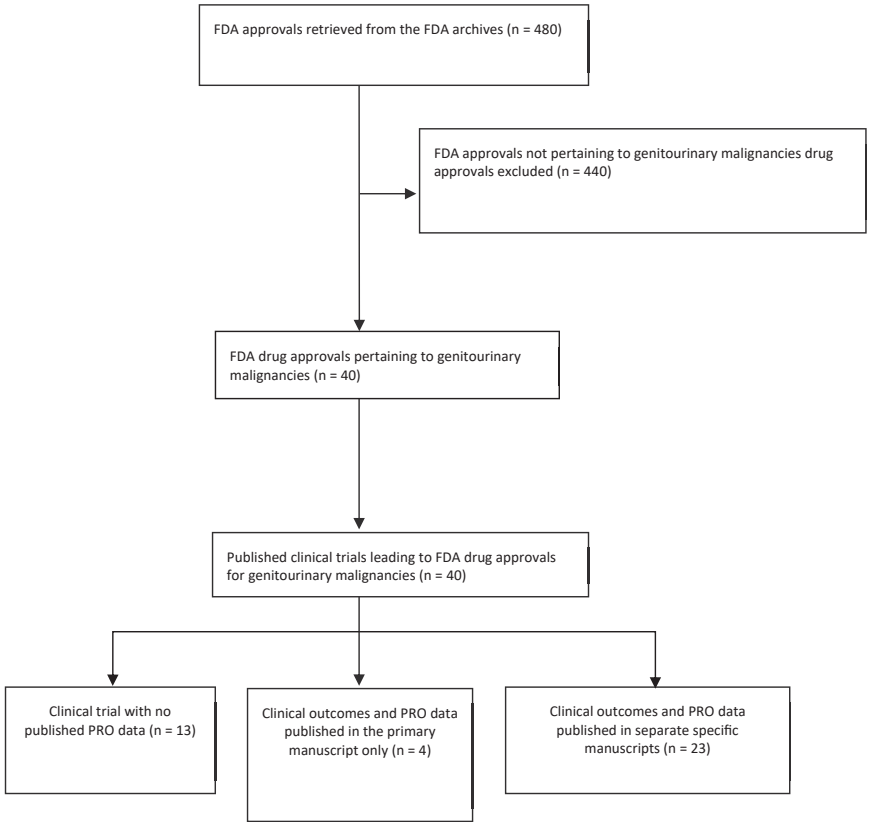

Fig. 1: Study selection flowchart for the identification, screening, and inclusion of studies. Abbreviations: FDA= Food and Drug Administration; PRO = patient reported outcome.

only used publicly available data without identifying patient information, an institutional review board approval was not required.

Data collection

The data collected satisfied a combination of previously peer reviewed evaluation criteria[37] and included our additional criteria to make a total of 47 predefined evaluation criteria (see Supplementary Table S1). Authors (M.P., H.S., M.T., V.J.) independently evaluated all selected protocols and publications. When opinions differed on how a criterion should be coded for a study, the criterion definition was further clarified, and authors resolved this by consensus after discussion with co-authors. We included information regarding PRO reporting and statistical analysis from the protocol, statistical analysis plan, and clinical study report. If discrepancies were found among the documents, then information was taken in the following order: the clinical study report first, the statistical analysis plan second, and the trial protocol third.

Quantitative PRO scoring system

We used the 24-point PROEAS quantitative scoring scheme to evaluate the quality of PRO reporting and analysis, per Safa and colleagues in 2021 (34). These items were derived from the recommendations of the 2020 SISAQOL Consortium (Supplementary Table S2). Each item was equally weighted and scored "1" if it was clearly reported, and "0" if it was either unclear or not reported, for a total maximum score of 24 points. We describe the PROEAS data using the interquartile range of the score, and also analyze the PROEAS categories to determine the most and the least reported items in the published PRO papers.

Statistical analysis

We used descriptive statistics with means, medians, and ranges for continuous variables and frequencies and percentages for categorical variables. All descriptive statistics for PRO publications characteristics were prespecified. Additionally, we conducted an exploratory analysis investigating the association between the likelihood of publishing PROs according to the following variables: type of therapy, clinical trial phase, number of study arms, type of FDA approval, type of cancer, approval indication, and type of primary endpoint of the trial. The χ^2 and Fisher exact tests were then used to compare categorical variables and the two-sample t-test and Wilcoxon rank sum test were used for quantitative variables. Two-sided P value of less than .05 was considered statistically significant. All statistical analyses were conducted using SPSS (Version 25.0, IBM Corp, Armonk, NY) and R version 4.2.1.

Ethics statement

This study used published data from existing studies. The requirement for ethical approval and informed consent was waived for this study.

Role of the funding source

There was no funding source for this study. All authors had access to the data and all authors were responsible for making the decision to submit this manuscript.

Results

PRO publications

Our search identified 40 clinical trial protocols leading to 40 FDA drug approvals for GU malignancies. A total of 27,011 participants were enrolled in these trials with 16,135 participants in the experimental arm and 10,876 in the control arm. The number of patients that were enrolled in each trial ranged from 96 to 1509. The median sample size was 690 patients (Q1–Q4: 420.75–1094, IQR: 673.25). Detailed characteristics of each clinical trial are summarized in Supplementary Table S3. Out of the 40 pivotal trials, thirty-two (80%) led to regular approvals, eight (27%) led to accelerated drug approvals (Table 1). Prostate cancer was the tumor type with the most reported studies for approval [16/40 (40%)], followed by renal cell carcinoma [14/40 (35%)], and lastly, urothelial carcinoma [10/40 (25%)]. Most of the FDA approvals were based on RCT's [31/40 (77.5%)] of which 11/31 (35%) were hormonal therapy approvals, 10/31 (31%) were targeted therapy approvals, 7/31 (22.5%) were immune based therapies, 2/31 (6.6%) radio-pharmaceutical approvals, and 1/31 (3%) was a chemotherapy-based approval.

PRO data were published for only 27 of the 40 [67.5%] trial publications supporting the FDA approvals, including 4 studies (4 of 40 [10%]) that reported preliminary PRO results in the primary clinical outcomes publication only and 23 studies (23 of 40 [57.5%]) that reported PRO data in a secondary dedicated publication. Among the 40 trials included in our cohort, 31 (77.5%) planned to collect PRO data (as reported in the trial's protocol or in the methods section of the primary clinical outcomes manuscript or on clinicaltrials.gov) and 9 (22.5%) did not. Of the 31 that planned to collect PRO data, 27 (87%) reported PRO results and 4 (13%) did not provide data within the timeframe of this study. The median time between primary clinical outcomes publications and their corresponding secondary PRO publication was 10.5 months (Q1–Q3: 7.25–18.5 months; IQR: 11.25 months). Trial publications supporting regular FDA approvals were more likely to have published PRO data than were those supporting accelerated FDA approvals (65% vs 2.5%, respectively; P = 0.001) (Supplementary Table S4). Similarly, among different trial phases, phase III was the most likely to publish PRO results (P = 0.001). Supplementary Table S5 shows a side-by-side comparison of reporting characteristics between PRO data published in a secondary dedicated manuscript and those published only in the primary manuscript. Furthermore, no correlation or difference of PRO score in relation to publication year before and after publication of SISAQOL (2020) was noted (Supplementary Figures S1 and S2).

Trial characteristics	n (%)
Approved therapy	
Targeted therapy	12 (30)
Immune-checkpoint inhibitors	12 (30)
Androgen receptor inhibitors	11 (27.5)
Radiopharmaceuticals	2 (5)
Cytotoxic chemotherapy	1 (2.5)
Other monoclonal antibodies	2 (5)
Approval type	
Regular	32 (80)
Accelerated	8 (20)
Approved indication	
First line	14 (35)
Second line and beyond	24 (60)
Maintenance	1 (2.5)
Adjuvant	1 (2.5)
Trials with single drug approvals	24 (60)
Trials with drugs approved in combination	16 (40)
Years of FDA approvals	
2007–2010	6 (15)
2011–2015	6 (15)
2016–2018	12 (30)
2019–2022	16 (40)
Tumor type	
Prostate cancer	16 (40)
Urothelial cancer	10 (25)
Renal cell cancer	14 (35)
Phase of published trial leading supporting the approval	
Phase 1	1 (2.5)
Phase 2	9 (22.5)
Phase 3	30 (75)
Randomization status of published trial supporting the approval	
Randomized clinical trial	31 (77.5)
Single-arm clinical trial	9 (22.5)
Supporting trial published data on PRO	27 (67.5)

Table 1: **Characteristics of clinical trial publications (n = 40) leading to GU cancer drug approvals.**

PRO characteristics	n (%)
PRO publication year	
2008–2010	3 (11)
2013–2014	5 (18.5)
2016–2018	6 (22)
2019–2020	4 (14.8)
2021–2022	9 (33.3)
Journal impact factor at time of publication	
<10	4 (14.8)
10–20	3 (11)
>20	20 (74)
PRO stated as an endpoint	
Primary endpoint	0
Secondary endpoint	14 (52)
Exploratory endpoint	10 (37)
Unclear PRO endpoint	3 (11)
PRO hypothesis	
Specific	0
Broad	19 (70)
Not reported	8 (30)
PRO instruments	
PRO instruments	
EQ-5D	21 (77.7)
FACT-P	13 (48)
BPI-SF	8 (30)
EORTC QLQ-C30	7 (26)
FKSI-DRS	6 (22)
EORTC QLQ-PR25	3 (11)
FKSI-19	3 (11)
BFI	2 (7)
FACT-G	2 (7)
EQ-VAS	2 (7)
Site-specific PRO instrument	23 (85)
Reference of the PRO instrument provided	22 (81)
Data collection	
PRO collection method	
Electronic	6 (22)
Paper	6 (22)
Not reported	15 (56)
Time point assessment	
Baseline time point collected	26 (96)
Two or more follow-up time points collected	25 (93)

[a]EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-core questionnaire; EORTC QLQ-PR25 = EORTC QLQ-Prostate Cancer Module; EQ-5D = EuroQol-5D; EQ-VAS = EQ visual analogue scale; FACT-G = Functional Assessment of Cancer Therapy: General; FACT-P = FACT-Prostate; FKSI-19 = Functional Assessment of Cancer Therapy—Kidney Symptom Index; FKSI-DRS = Functional Assessment of Cancer Therapy—Kidney Symptom Index—Disease Related Symptoms; BPI-SF = Brief Pain Inventory-Short Form; BFI = Brief Fatigue Inventory.

Table 2: **Characteristics of included PRO publications and their PRO data collection methods (n = 27).**[a]

Patient reported outcomes characteristics

The PRO characteristics are reported in Table 2. Among the 27 studies that published PRO data, PRO data were never reported as primary endpoints of the study. Most PRO were studied as secondary endpoints (14/27 [52%]), while others were studied as exploratory endpoints (10/27 [37%]). Three (11%) studies did not specify the PRO endpoints. RCT's were more likely to publish PRO data than non-randomized controlled trials (62.5% vs 5.0%, respectively, P = 0.001). Most [23/27 (85%)] of PRO data were published in journals with an impact factor >10.

PRO instruments and schedule

The studies employed various standardized questionnaires to assess the QOL of participating patients. Some focused on specific malignancies, while others had a more general approach (see Table 2). The most frequently used questionnaire, utilized in 21 studies

(78%), was EuroQol-5 (EQ-5D), which evaluated general QOL across different malignancies. The second most used questionnaire was the Functional Assessment of Chronic illness therapy (FACT). FACT-G, used in two studies, is the original general questionnaire and FACT-P, used in 13 studies 13/27 (48%) is a modified disease specific questionnaire that directs QOL questions regarding prostate cancer specifically. Other general questionnaires used include: EORTC Quality of Life Questionnaire (EORTC-QLQ-C30) [7/27 (26%)], Bowel Function Instrument (BFI) [2/27 (7%)], Brief Pain Inventory Short Form (BPI-SF) [8/27 (30%)}, and EuroQol —Visual Analogue Scale (EQ-VAS) [2/27 (7%)]. Functional Assessment of Kidney Symptom Index (FKSI) was another cancer specific questionnaire that was used in 9 studies [9/27 (33%)].

Statistical analysis and clinical relevance

We found variations in the statistical tests and analyses conducted on the published PRO data. Only 13 of the 27 studies (48%) specified a predetermined time point for comparing PRO data. While most trials included baseline assessments and follow-ups at multiple intervals, only 14 of 27 papers (52%) reported questionnaire completion and compliance rates at both baseline and subsequent time points. The definition of clinical relevance varied among the publications, the most commonly used was "a change of X points from baseline within a patient or within a treatment group", 21 of 27 papers (78%) provided a specific definition. Different statistical techniques were employed for analyzing PRO data, including four methods for time-to-event analysis and five methods for assessing change from baseline. Details can be found in Table 3. Despite testing multidimensional endpoints and evaluating multiple time points, only 3 of 27 studies (11%) performed a correction for multiple testing to control for Type I error.

Missing data, limitations and conclusions

Reasons for missing data included disease progression, death, or treatment discontinuation. In 19 of 27 studies (70%), the protocol documented the planned approach for handling missing data in the primary analysis. Only 13 studies (48%) specified multiple approaches for handling missing data. However, 7 papers (26%) did not address at all the limitations associated with assessing and analyzing missing PRO data. Further details on missing data and limitations can be found in Table 3. Regarding conclusions, 2 of 27 single-arm studies (8%) reported either improvements or stability in key PROs after treatment initiation. The majority of RCTs, 18 of 27 studies (67%), concluded that PRO findings in the experimental arm were superior to those in the control arm.

PROEAS ratings

Of the 30 RCTs in our dataset, 20 (66%) published PRO data in a dedicated secondary manuscript. Table 4 details the number of studies that reported each item of the PROEAS. Among these 20 RCTs, 11 (55%) focused on prostate cancer, 7 (35%) on kidney cancer, and the remaining 2 (10%) on urothelial cancer (Fig. 2). The scores for the selected trials ranged between 6 and 17 points out of 24, with a mean score of 11.10 points (range: 6–15). More than half of the studies had a score of 12 or less (13 of 20, 65%). All studies appropriately reported PRO endpoints in the clinical trial protocol. In contrast, none of the studies provided a definition for missing data in the trial protocol.

The subcategory with the lowest score was "Standardizing statistical terms related to missing data," with a mean score of 2.15 on a 6-point subscale (range: 0–4). The second lowest score was in the "General handling of missing data" subcategory, with a mean score of 2.25 on a 5-point subscale (range = 1–4, SD). Only 6 out of 11 prostate cancer studies (55%) and 2 out of 7 kidney cancer studies (29%) documented the approach for handling missing data in the trial protocol. The "taxonomy of research objectives" subcategory mean score was 3.55 (range: 1–5) on a 7-point subscale. Only 1 out of the 20 RCTs (5%) prespecified the clinical relevance for between-group differences in the trial protocol.

The "recommending statistical methods" subcategory mean score was 4.10 (range = 0–6) on a 6-point subscale. In this subcategory score, 18 of 20 RCTs (90%) used at least one appropriate statistical test to evaluate the tested PRO endpoint. None of the PROs met all the criteria recommended by the SISAQOL Consortium.

Discussion

In this comprehensive study, we shed new light on the specifics of PRO endpoint design, conduct and reporting methods of FDA-approved drugs for GU cancers over the past 15 years. Our data showed a considerable gap in the reporting of PROs and in the quality of design and conduct of PRO related trial endpoints. In fact, only two third of the trial publications supporting FDA approvals (27 of 40, 67.5%) included and published PROs related study results, with an average of 10 months delay from the primary publication underscoring a critical issue. We also noted that 10% of studies (4 of 40, 10.0%) solely published preliminary PRO results in primary clinical outcomes manuscripts and noted a significantly higher probability of publishing PROs data in trial that received regular FDA approval in comparison to those with an expedited approval (65% vs 2.5%, respectively; P = 0.001). Even though, the timely and concordant publication of PROs related results with the study primary clinical outcomes, the PROs methodology and results need to be fully presented with all the needed details to allow readers to draw rigorous scientific conclusions.[38] Although the CONSORT-PRO guidelines recommend incorporating primary and secondary PRO

Variable	n (%)
Data reporting	
Definition of study population	
Patients with a baseline assessment and at least 1 postbaseline assessment	3 (11)
Intent to treat	11 (40)
Patients who received at least 1 dose of study medication and completed at least 1 assessment	3 (11)
Not clearly defined	10 (37)
PRO completion rate	
Completion/compliance rate table included in the manuscript	14 (52)
Clinical relevance threshold was prespecified as	
Change of X points from baseline within-patient or treatment group	12 (44)
Difference of X points between arms at a certain timepoint	9 (33)
Both	0
Not reported	6 (22)
Clinical relevance was justified and cited[a]	18 (67)
Data analysis	
Primary statistical technique	
Time-to-event analysis	
Kaplan–Meier model	13 (48)
Cox proportional hazard/Cox regression model	8 (30)
Log rank test	5 (19)
Brookmeyer and Crowley[b]	1 (4)
Magnitude of change from baseline analysis	
Mixed model for repeated measures	19 (70)
cLDA/LDA	1 (4)
Mixed effects model	1 (4)
t tests	1 (4)
Chi-square	1 (4)
PRO scores were compared at baseline between 2 arms	17 (63)
Control for type I error	3 (11)
PRO data analysis stratified by ethnicity/race	0
Handling of missing data	
Strategy to deal with missing data is defined[c]	19 (70)
Detailed reasons for missing data by timepoint reported	1 (4)
PRO specific limitations stated in the discussion section	20 (74)
PRO conclusion	
Experimental arm is superior to control arm	18 (67)
Similar outcomes between experimental arm and control arm	6 (22)
Improvement in key PROs[d]	1 (4)
Stable PROs[c]	1 (4)
Experimental arm is inferior to control arm	0
Not reported	1 (4)

[a]Articles that did not justify clinical relevance where those that did not specify the clinical relevance. Numbers are rounded to the nearest whole number. cLDA = constrained LDA; LDA = longitudinal data analysis. [b]KARRISON T. Confidence intervals for median survival times under a piecewise exponential model with proportional hazards covariate effects. Statistics in medicine. 1996 Jan 30; 15 (2):171–82. [c]Two manuscripts stated that the approach to deal with missing data was "no imputations" and 1 stated that the approach to deal with missing data was "left as missing." [d]Single-arm studies.

Table 3: **Data reporting, clinical relevance, and statistical analysis methods used for PRO data (n = 27).**

outcomes in the main trial manuscript, there is encouragement to publish additional PRO endpoints, such as exploratory measures and parts of composite PRO scores, in online supplements alongside primary clinical outcomes.[33] Lastly, most publications were in high impact journals (85% of publications in journals with IF >10) indicating a high level of readership interest and general support from scientific journal editor to the dissemination of the PROs data from GU cancers trials.

Notably, while some trials did not plan PROs as primary or secondary trial endpoints, the vast majority intended to collect PRO data but failed to report them, indicating a systemic reporting challenge of timely and

Variable	N (%) or mean (range)
PRO endpoints were specified in the protocol (1 point)	20 (100)
Hypothesis requirement was met as needed (1 point)	11 (55)
Endpoints were used to make appropriate conclusions (1 point)	11 (55)
Direction of the hypothesis was prespecified in the protocol if required (1 point)	11 (55)
Clinically relevant margins for significant between-group differences were prespecified in the protocol (1 point)	1 (5)
Within-treatment group objective stated in the protocol (1 point)	8 (40)
A clinically relevant within-patient or within-treatment group change or stable state was predefined in the protocol (1 point)	9 (45)
Taxonomy of research objectives subscore (7 points)	**3.55 (1.00, 5.00)**
Statistical test comparing two groups done when appropriate (1 point)	17 (85)
Was P value provided (1 point)	16 (80)
Test used adjusted for baseline co-variates (1 point)	11 (55)
Handled clustered data (repeated assessments) (1 point)	19 (95)
Correction for multiple testing done appropriately (1 point) In methods they adjusted for multiple testing or fixed the type 1 error	3 (15)
Used at least 1 appropriate statistical test to evaluate the tested outcome (1 point)	18 (90)
Recommending statistical methods subscore (6 points)	**4.10 (1.00, 6.00)**
A definition for missing data was reported (1 point)	0
Study did not consider PRO assessments for deceased patients as missing data (1 point)	6 (30%)
Fixed denominator rate reported (1 point)	6 (30)
Variable denominator rate reported (1 point)	9 (45)
Absolute numbers for both numeratory and denominator reported (1 point)	9 (45)
A CONSORT diagram or table reporting reasons (1 point)	13 (65)
Standardizing statistical terms related to missing data subscore (6 points)	**2.15 (0.00, 4.00)**
Study documented a-priori the missing data approach that will be used for the primary analysis in the protocol (1 point)	8 (40)
Item-level missing data within a scale were handled according to the scoring algorithm developed during the scale's development (1 point)	11 (55)
A method that allows the use of all available data was used to approach missing data (1 point) likelihood-based test	3 (15)
Study did not use explicit imputation methods unless justified (1 point) simple imputation = 0 multiple imputation = 1	17 (85)
At least two different approaches to handle missing data were used (1 point)	6 (30)
General handling of missing data subscore (5 points)	**2.25 (1.00, 4.00)**
Total score (24 points)	11.10 (6.00, 15.00)

CONSORT = Consolidated Standards of Reporting Trials.

Table 4: **PROEAS item reporting for randomized clinical trials (n = 20).**

detailed PRO data. This should be a focus for improvement for regulator, industry partner and trials principal investigators.

Our review also showed a significant degree of variability across studies concerning first the lack of a specific hypothesis driven PRO endpoint, second the selection of appropriate statistical tests and methodologies employed for PRO endpoints. This heterogeneity poses challenges when attempting to consolidate evidence related to PRO measures in the context of various therapeutic interventions, thus limiting the capacity of the medical community to make meaningful comparisons between trials with drug approvals for similar indications. In clinical trials with the absence of a well-suited statistical approach tailored to the defined endpoint and hypothesis, there is a heightened risk of misinterpreting the data.[39] Particularly, when PROs are designated as exploratory endpoints, the use of quantitative statistics for drawing definitive conclusions becomes inappropriate. Therefore, the use of descriptive statistics should be considered a minimum requirement for the reporting of such data.[40] It is noteworthy that in our study, a third of RCTs (10 of 27, 37%) PROs were reported as exploratory endpoints, underscoring the need for caution in overinterpreting these studies findings and associate P values. This discrepancy in reporting aligns with findings from other reviews examining the state of statistical reporting of PRO measures in clinical trials of various cancer treatments.[27,28,41–43] To address this issue, establishing clear hypothesis driven statically powered endpoints and a prospective framework for PRO measures during the planning phase of clinical trials will significantly enhance the quality of evidence and interpretation.

Pe et al., in 2018 and Fiero et al., in 2019 published studies addressing PRO reporting in breast and lung cancer drug trials respectively.[9,37] Our observations in GU studies concur with both papers regarding the desynchrony in reporting of PRO. Efforts to standardize the methods to handle and analyze PRO data resulted in the publication of guidelines and recommendations by the SISAQOL Consortium regarding the existing gap

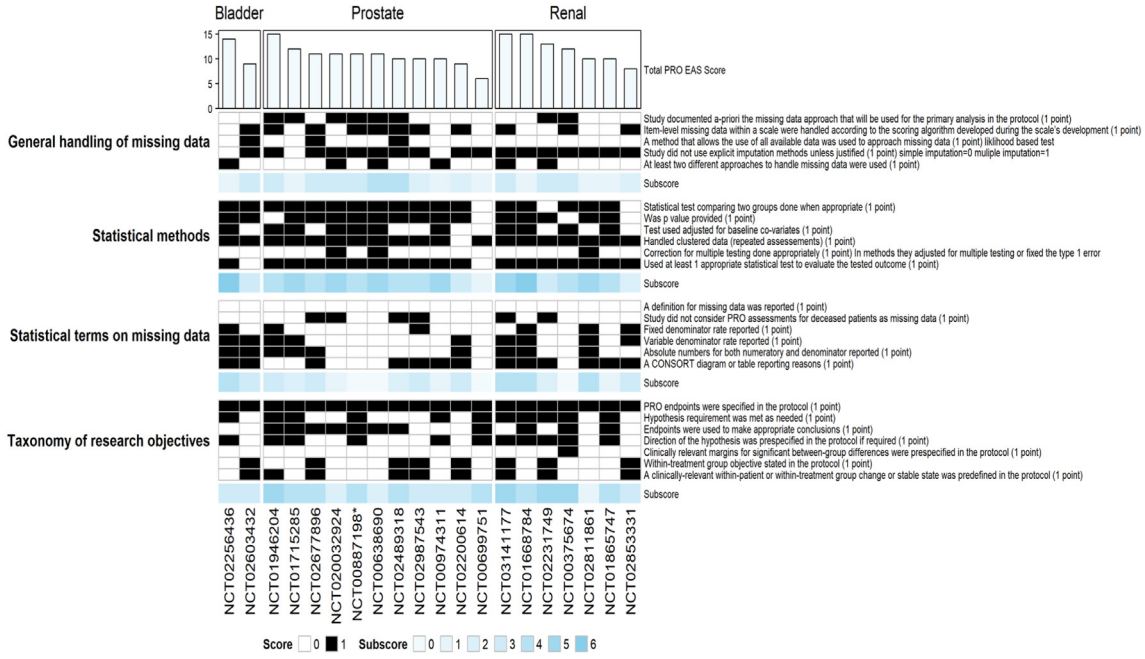

Fig. 2: PROEAS graph reporting the different PROEAS scores per category for randomized clinical trials individualized by GU tumor type. Abbreviations: PROEAS: Patient Reported Outcome Endpoint Analysis Score; GU: genitourinary.

in this area of RCTs.[20] Using the PROEAS, our data showed that none of the RCTs met all of the recommendations of the SISAQOL Consortium, and more than half of the studies (13 of 20, 65%) had a score of 12 or less. We did not note significant differences in the median total scores of RCC trials in comparison to bladder cancer or prostate cancer trials. The most deficient subcategory scores were related to the definition and handling of missing data. According to the SISAQOL Consortium recommendations, missing data should only include data that are meaningful for testing a certain prespecified hypothesis but were not collected.[20] The abundance of missing data, the absence of a clear definition for what are considered missing data, and the poor handling of missing data weaken the statistical significance of PRO findings and may discredit the stated conclusions.[44,45]

With the advent of targeted therapies and immunotherapies, the treatment landscape for urothelial and renal cell carcinomas has undergone notable transformation.[46,47] Recent approvals in genitourinary (GU) cancers have introduced novel therapies, and the emergence of radionuclide therapy has shown promise, particularly in cases of metastatic prostate cancer. These novel therapies are associated with different drug related adverse events and potential improvement in patients' quality of life, that requires optimization in capturing PRO measurement in a standardized manner. With the expanding array of therapies for GU malignancies, the accessibility and clear presentation of PRO data are also essential for tailoring personalized treatment plans for patients, highlighting the crucial need for improved reporting and accessibility of this information.

The retrospective data collection of only the clinical trials cited in the FDA approval is a limitation of our study. The authors, aimed to limit our analysis to these trials only to reflect the information available for regulators to render their approval decision. We acknowledge, the limitation that additional clinical trials could have been not included in certain circumstances where these studies assessed the same drug indication but were not included in the FDA approval submission by the drug manufacturer. Also, PROEAS was assessed only for RCT's as non-RCTs were less likely to publish PRO data as these types of trials were using a less stringent scientific methodology for the study primary endpoint in comparison to RCTs. Another major limitation is the difficulty in accessing all the different study protocols versions, which hindered the validation of data from the publications. The authors acknowledge that trials protocols have multiple amendments, for that reason we included the final version of the protocols that was available to us at the time of our study conduct.

Our study found heterogeneity in the design, reporting, analysis, and methodologies used for PRO reporting in GU cancer drugs. It is crucial to enhance efforts to ensure timely and high-quality reporting of PROs for FDA-approved drugs. Although a speculation on to what extent PRO results contributed to the final

FDA approval cannot be made, we hope that in the future such inference could be made by the regulatory bodies in the US and Europe. Future clinical trials should also prospectively establish PRO hypotheses, primary or secondary endpoints, statistical analysis methods, and approaches to handle missing data per the published SISAQOL guidelines to ensure meaningful and translational results that will impact patient centered care.

Contributors

JC, MP, HS, YK had full access to all the data in the study and take responsibility for the integrity and the accuracy of the data analysis. Study concept and design: HS, MT, MP, JC. Acquisition of data: HS, MT, JSC, JJA, VJ. Analysis and interpretation of data: HS, MT, MP, VJ, DK, YK. Drafting of the manuscript: HS, VJ, MP, JC. Critical revision of the manuscript for important intellectual content: MP, HS, VJ, MT, JJA, FI, SS, SG, BJM, AS, HSJ, PES, JC. Administrative, technical, or material support: JC. Study supervision: JC. All authors read and approved the final manuscript.

Data sharing statement

All data derived from this study are in the article, further inquiry about the data can be made to the corresponding author who will provide additional data upon specific request.

Declaration of interests

Nothing to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102413.

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