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Review Article

Assessing patient-reported outcomes (PROs) and patient-related outcomes in randomized cancer clinical trials for older adults: Results of DATECAN-ELDERLY initiative

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ABSTRACT

As older adults with cancer are underrepresented in randomized clinical trials (RCT), there is limited evidence on which to rely for treatment decisions for this population. Commonly used RCT endpoints for the assessment of treatment efficacy are more often tumor-centered (e.g., progression-free survival). These endpoints may not be as relevant for the older patients who present more often with comorbidities, non–cancer-related deaths, and treatment toxicity. Moreover, their expectation and preferences are likely to differ from younger adults.

The DATECAN-ELDERLY initiative combines a broad expertise, in geriatric oncology and clinical research, with interest in cancer RCT that include older patients with cancer. In order to guide researchers and clinicians coordinating cancer RCT involving older patients with cancer, the experts reviewed the literature on relevant domains to assess using patient-reported outcomes (PRO) and patient-related outcomes, as well as available tools related to these domains.

Domains considered relevant by the panel of experts when assessing treatment efficacy in RCT for older patients with cancer included functional autonomy, cognition, depression and nutrition. These were based on published guidelines from international societies and from regulatory authorities as well as minimum datasets recommended to collect in RCT including older adults with cancer. In addition, health-related quality of life, patients' symptoms, and satisfaction were also considered by the panel. With regards to tools for the assessment of these domains, we highlighted that each tool has its own strengths and limitations, and very few had been validated in older adults with cancer. Further studies are thus needed to validate these tools in this specific population and define the minimum clinically important difference to use when developing RCTs in this

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population. The selection of the most relevant tool should thus be guided by the RCT research question, together with the specific properties of the tool.

1. Introduction

More than half of patients diagnosed with cancer are aged 65 and over and this trend is going to increase as the world population ages [1,2]. However, there is limited evidence on which to base treatment decisions for older adults with cancer, mainly because they are underrepresented in the randomized clinical trials (RCTs) that set the standards for cancer treatments [3]. Although the proportion of older adults included in RCT remains lower than the proportion they represent in the general population, this proportion as well as the number of trials dedicated to older adults has been increasing over the last years [4].

Literature reviews on endpoints in cancer RCTs dedicated to older adults have highlighted the lack of consideration of patient-reported outcomes (PROs). A PRO is an outcome directly reported by the patient without interpretation of the patient's response by a clinician or anyone else, and pertains to the patient's health, quality of life (QoL), or functional status associated with health care or treatment [5]. A typical PRO example is the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire (QLQ-C30) [6], a self-reported questionnaire aimed at assessing health-related quality of life (HRQoL) of patients with cancer. Following the Clinical Outcome Assessment (COA) framework of the Food and Drug Administration (FDA) [7], PROs are considered as part of the family of COA measures, defined as measures that describe or reflect how a patient feels, functions, or survives. COAs include PRO measures, observer-reported outcome (ObsRO) measures, clinician-reported outcome (ClinRO) measures, as well as performance outcome (PerfO) measures. An ObsRO is a measurement based on a report of observable signs, events, or behaviors related to a patient's health condition by someone other than the patient or a health professional. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life. They do not rely on medical judgment or interpretation and include rating scales such as the Instrumental Activities of Daily Living (IADL) [8]. On the other hand, a ClinRO is a measurement based on a report that comes from a trained health-care professional after observation of a patient's health condition. Most ClinRO measures involve a clinical judgment or interpretation of the observable signs, behaviors, or other manifestations related to a disease or condition. ClinRO include reports of particular clinical findings or clinical events, as well as rating scales such as the Geriatric Depression Scale - 15-item (GDS-15) [9]. Finally, PerfO are measurements based on standardized tasks actively undertaken by a patient according to a set of instructions. Examples of PerfO assessments include measures of gait speed or memory (e.g., word recall test).

Throughout the rest of this manuscript and for ease of exposition, we will refer to PRO (directly reported by the patient), patient-related outcomes (for ObsRO or ClinRO rating scales), and performance measures (PerfO).

Although PROs and patient-related outcomes are more frequently used in RCTs dedicated to older adults than in RCTs including all patients with cancer, they still represent a small proportion of efficacy endpoints, in particular primary endpoints [4,10]. Studies have reported that PROs represent <10% of primary endpoints and near 40% of secondary endpoints [4,11].

In order to increase the use of PROs and patient-related outcomes and properly assess treatment outcomes in RCTs including older adults, one must first identify the appropriate geriatric domains and the relevant tools for the assessment of each of these domains. Thus, this article aims to present the geriatric domains that should be assessed using PROs and patient-related outcomes and an extensive review of available tools related to these domains, bringing clear elements to guide the choice of researchers coordinating cancer RCTs involving older patients.

The manuscript proceeds as follows: we first describe the working group, then provide an overview of published guidelines (scientific societies, regulatory authorities, minimum datasets), present relevant tools for outcome assessment, discuss statistical issues, trial protocol and reporting, and then conclude with a general discussion.

2. The DATECAN-ELDERLY Working Group

The DATECAN-ELDERLY project was launched following the international DATECAN initiative that was initiated in 2009 with the objective of elaborating standardized definitions for survival endpoints in RCTs, based on a rigorous and validated consensus methodology. This collaborative work involved the network of statisticians from French Regional Comprehensive Cancer Centers, the network of the Cancer Data Centers, as well as the EORTC. After properly defining the methodology [12], guidelines for the definition of time-to-event endpoints to be used in randomized trials for specific cancer sites were developed [13] [14] [15] [16], and are ongoing for additional cancer sites. These guidelines reported on tumor-centered endpoints (e.g., disease-free survival, time-to-treatment failure). Recommendations as to which clinical event(s) to include for each time-to-event endpoint were produced. One can thus refer to these guidelines when designing an RCT for the older population with tumor-centered outcomes. Patient-centered outcomes, on the other hand, had not been addressed up to date.

The DATECAN-Elderly project was thus launched to provide guidelines on geriatric domains, as well as PROs and patient-related outcomes to be considered when designing RCTs for older adults with cancer. In this population, it is relevant to go beyond the question of which event to include as endpoint. Indeed, it is necessary at first to define which domains to consider when assessing treatment benefit, and then to retrieve available relevant tools. The present work is thus aimed at identifying relevant domains of interest and providing an overview of PRO and patient-related outcome tools, to guide researchers when conducting clinical trials in older adults with cancer.

A working group made up of an international multidisciplinary panel was set up, involving experts in medical oncology (PS, EB, RK, SM, HW), geriatrics (MH, SR), nursing (MP), surgery (KLC, IM), epidemiology (AG, SMP), and biostatistics (CB, MM), as well as representatives of the DATECAN-initiative (CB, SMP).

The discussion content was separated in two parts: (i) selection of the relevant domains to consider when assessing treatment benefit in older adults with cancer and (ii) identification of available tools to assess these domains.

As regards to domains of relevance, a review was conducted (AG, CB) focusing of guidelines from international societies and regulatory authorities as well as minimum datasets recommended to collect in RCT including older adults with cancer. A summary of this review was presented and discussed with all the experts (Visio conference, March 2022, 11 experts). The experts commented and enriched this review, and then provided recommendations. Experts not present at the meeting provided their feedback subsequently, following the minutes of the meeting.

As regards to available tools, a narrative review was first conducted (AG, CB) and relevant criteria to guide the choice of one tool over another were discussed with the experts. Investigated criteria included: objective of the tool, number of items, interpretation of the score, initial target population and subsequent populations, validation available for older adults and/or adults with cancer and/or older adults with cancer, available translations, minimum clinically important differences (MCIDs), fees, and copyright. A draft document listing these characteristics for all available tools was circulated to the experts who could

enrich and comment the document. The final draft document was finally approved by all experts.

3. Domains of Relevance

In order to identify the relevant domains, the working group considered guidelines from international societies and regulatory authorities as well as minimum datasets recommended to collect in RCT including older adults with cancer.

3.1. International Societies

Several international societies have issued recommendations aimed at improving the evidence for the treatment of older patients with cancer by increasing their enrollment in RCT and improving trial design.

In a joint paper published in 2013, the EORTC, the Alliance for Clinical Trials in Oncology, and the International Society of Geriatric Oncology (SIOG) underlined the need for appropriate endpoints and designs for clinical trials in older patients with cancer [17]. They presented a list of relevant endpoints in RCTs in the older cancer population including such patient-centered endpoints as HRQoL and maintenance of functional capacity/independence.

The American Society of Clinical Oncology (ASCO) published recommendations and action items for improving clinical research in older patients [18,19]. The society recommended the development of novel endpoints to compare efficacy and tolerability of the different cancer treatments [18]. Recommendations were also established on the importance of geriatric assessment in care including in particular the evaluation of functional status, falls, cognition, depression, and nutritional status [18,19].

3.2. Regulatory Authorities

The FDA published guidance on the inclusion of older adults in cancer clinical trials recommending the incorporation of PROs. They also recommended the collection of elements from geriatric assessment tools such as functional status, cognition, and frailty, as well as core PROs including disease-related symptoms, symptomatic adverse events, overall side effect impact summary measure, physical function, and role function [20,21]. The European Medical Agency (EMA) recommended including HRQoL and patient-reported symptom assessment in clinical trials and underlined the importance of functional status, depression, and cognitive functioning affecting HRQoL in older adults with cancer. They also recommended the assessment of baseline frailty using the Short Physical Performance Battery (SPPB) and the gait speed for the characterization of older adults in clinical trials [22].

3.3. Minimum Datasets to Collect in RCTs

Over the last years, there has been an increasing interest for developing a minimum dataset for assessing the global health of older adults with cancer participating in RCTs and harmonizing the collection of relevant data in this population.

The EORTC established a standardized Elderly Minimal Dataset (MinDS) including data collection on autonomy, cognition, depression, nutritional state, comorbidities, and social situation. The organization underlined the fact that the dataset does not need to be restrictive or comprehensive, but rather should form the backbone upon which investigators could add assessment tools that are relevant to their studies.

The DIalog for personALization of management in geriatric OncoloGy (DIALOG) intergroup established the Geriatric Core Data-set (G-CODE) by updating the EORTC initiative with the goal to describe more accurately the older population with cancer and to standardize geriatric data collection in clinical trials in a brief and practical way [23]. The G-CODE includes assessments on autonomy, cognition, depression, nutrition, comorbidities, and social situation.

Functional autonomy, cognition, depression, nutrition, HRQoL, and patients' symptoms and satisfaction were identified by either scientific societies or regulatory authorities, or were included in minimum datasets. Thus, the panel of experts considered these domains as relevant when assessing treatment benefit in older adults with cancer.

4. Relevant Tools for Outcome Assessment

Once relevant domains were identified, the panel of experts conducted a review to identify existing PRO and patient-related outcomes tools. Strengths and limitations of these tools are discussed below.

4.1. Functional Status

Functional impairment refers to deficits in a range of abilities affecting the needs of daily life. The occurrence of functional impairment increases with age and the presence of comorbidities. Functional impairment negatively affects HRQoL, increases the risk of institutionalization, emergency department admissions, and unplanned hospitalizations, and is associated with chemotherapy toxicity and shorter survival [24–26]. Studies have reported a prevalence of functional impairment in older adults with cancer ranging from 37% to 55% in activities of daily life, and from 30% to 67% in physical performance [27–29]. Knowing that older adults find maintaining their functional abilities an important consideration when deciding on their cancer treatment [30], functional impairment is a meaningful endpoint for RCTs in older adults with cancer. PROs, patient-related outcomes, and performance measures are recommended to evaluate functional status in older adults with cancer, and SIOG recently published an interprofessional report presenting the main tools with which to assess these [31].

PROs and patient-related outcomes allow reporting on the patient's ability to perform specific tasks (e.g., tasks of daily living). Several tools are available to evaluate functional status reported either by the patient or by the care provider (Table 1). The Activities of Daily Living (ADL) scale [32] and the Barthel Index [33] evaluate the ability to perform basic activities of daily living (e.g., feeding, bathing, dressing) allowing patients to care for themselves, while the IADL scale [8] evaluates the ability to perform more complex activities of daily living (e.g., taking medications, handling finances). ADL and IADL scales are recommended by ASCO and an MCID was recently defined for these scales in older adults [19,34].

Two physician-reported measurements of performance status (PS) are also widely used in oncology: the Eastern Cooperative Oncology Group Performance Status (ECOG PS) [35] and the Karnofsky Performance Status (KPS), [36] which describe a patient's level of functioning. Although they are simple and useful in a clinical setting, these PS measures present high interobserver variability and a moderate level of agreement with patients' evaluation, with healthcare professionals being more likely to record healthier performance status levels than patients themselves [37]. As they rely on a unique global assessment, these PS measurements may rate the patient as functionally normal and may miss important impairments identified by a geriatric evaluation [38].

Performance measures directly assess the patients' ability to perform specific tasks. Several performance measures are commonly used to measure functional status, such as the Timed-Up and Go (TUG) [39,40], the Hand Grip Strength (HGS) [41], and the SPPB [42]. They aim to assess balance, physical mobility, and physical function of upper or lower extremities. The MCID was calculated for these three performance measures, although data are not available for older adults with cancer specifically. Other performances measures as the gait speed, the Chair Stand Test and the 6-min walk test are also commonly used but are not further described as they are mainly parts of the SPPB.

PROs, patient-related outcomes, and performance measures provide complementary information and are not mutually exclusive. Self-reported measurements may identify changes at lower levels of

Table 1
Self-reported measurements of functional status.

Tool name	Aim	Description and score interpretation	Cognitive domains	Initial population	Validated in			Available in several languages (*)
					Older adults	Patients with cancer	Older adults with cancer	
ADL [32]	To assess older adults' ability to perform activity of daily living independently	6-item questionnaire Score range: 0 (totally dependent) to 6 (totally independent)	Bathing, dressing, toileting, transferring, continence, feeding	Older adults	Yes	*NA*	(**) [19]	Yes
Barthel index [33]	To measure performance in activities of daily living	10-item questionnaire Score range: 0 (totally dependent)-100 (independent)	Feeding, toileting, bathing, dressing and undressing, getting on and off a toilet, controlling bladder, controlling bowel, moving from wheelchair to bed and returning, walking on level surface, ascending and descending stairs	Chronic patients	Yes	Yes	No	Yes
IADL [8]	To assess older adult's ability to perform instrumental activity of daily living independently	8-item questionnaire Score range: 0 (totally dependent) to 8 (totally independent) for women, 0 (totally dependent) to 6 (totally independent) for men	Using the telephone, shopping, cooking, doing housekeeping, doing laundry, taking medications, using transportation, managing finances	Older adults	Yes	*NA*	(**) [19]	Yes
ECOG PS [35]	To measure functional status	1-item scale, 6-point rating Score range: 0 (fully active)-5 (dead)	General functional status	Patients with cancer	*NA*	Yes	No	Yes
KPS [36]	To measure functional status	1-item scale, 11-point rating Score range: 0 (dead)-100 (normal functioning)	General functional status	Patients with cancer	*NA*	Yes	No	Yes

Abbreviations: ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; ECOG PS, Eastern Cooperative Oncology Group Performance Status; KPS, Karnofsky Performance Status; NA, Not applicable given the initial validation population.
(*) Unknown number of available translations.
(**) Experts consensus stating that the questionnaire can be used in older adults with cancer [19].

function that would not be detected during a clinical consultation (e.g., bathing, dressing) while performance measures may identify changes at a higher level of functioning sooner (e.g., impaired balance). Thus, combining approaches may be more informative [43].

4.2. Cognition

Due to its prevalence in older adults, cognitive impairment (from mild impairment to dementia) also represents an important challenge in older adults with cancer. In two recent clinical trials dedicated to patients with cancer aged 70 and over, 21% to 36% of them screened positive for cognitive impairment or dementia [44–47]. Cancer diagnosis and cancer treatment may have impacts on cognition; studies report cancer-related cognitive impairment associated with cancer treatment but also to cancer itself [48]. Thus, there is a clinical and scientific interest to evaluate cognition as an endpoint in RCT, also knowing the importance for older patients to maintain their cognitive capacities.

Different tools were recommended to evaluate cognition in older adults with cancer [23,49–51] (Table 2). The Mini-Mental State Examination (MMSE) [52] and the Montreal Cognitive Assessment (MoCA) [53] require 10 to 15 min to be administered by the care-provider and consist of a 30-item questionnaire. These patient-related measures are available in many languages and an MCID was set for both of them enabling the study of score change over time. While they are the most comprehensive tools covering a large range of cognitive domains, the MMSE does not assess executive function and the MoCA does not assess praxis. Another difference between these two tools lies on their purposes: the MMSE was developed for diagnosing dementia and is not good for identifying mild cognitive impairment, while the MoCa was designed for detecting mild cognitive impairment.

The other tools presented in this section, essentially considered as performance measures, cover fewer cognitive domains and are available in fewer languages, but do present some strengths. The Blessed Orientation-Memory-Concentration Test (BOMC) [54] is limited to three cognitive domains but has the main advantage of not being sensitive to the patient's educational level, whereas the other instruments are. The Clock-Drawing Test (CDT), which covers two cognitive domains via a nonverbal screening tool, does not require any translation, is easy to use, and requires a short administration time [55]. The main limitation of the CDT lies in the multiple available scoring and interpretation methods [56]. The mini-Cog [57], which incorporates the CDT in addition to three memory items, requires minimal language interpretation.

While the CDT has been validated in older patients with cancer [58,59], the MMSE has been validated in patients with cancer patients but not in older adults [60]. The MoCA and BOMC were not validated in patients with cancer, but feasibility studies have been performed in this population [61,62].

Despite the fact they have not been validated in older adults with cancer, the MMSE and the MoCA appear as the most appropriate tools to assess cognitive outcomes in this population considering the large cognitive domains they cover, the presence of a MCID, and available translations. However, further studies to validate these questionnaires in older adults with cancer are needed.

4.3. Depression

Depression is one of the most frequent causes of emotional distress in older adults, with a prevalence ranging from 4% to 23% in community dwelling adults and from 15% to 36% in primary care settings [63]. Depression is also one of the most common psychiatric symptoms experienced by patients with cancer, with a prevalence ranging from 3% to 31% depending on depression measurement method, cancer location, treatment status, and patients' age [64]. Depression is challenging to diagnose in patients with cancer mainly because of the overlap between the diagnostic criteria for depression and the symptoms often

Table 2
Cognitive assessment tools.

Tool name	Aim	Description and score interpretation	Cognitive domains	Initial population	Validated in			Available in several languages
					Older adults	Patients with cancer	Older adults with cancer	
MMSE [52]	To screen and monitor for cognitive impairment, dementia and delirium	30-item questionnaire Range score 0–30 points Score < 24: cognitive impairment BUT depending on age, sex and education	Memory, visuospatial, orientation, attention, language, praxis	General population	Yes	Yes	No	Yes, >50 languages
MoCA [53]	To screen for mild cognitive impairment	30-item questionnaire Score range 0–30 points Score ≤ 26: cognitive impairment BUT depending on age, sex and education	Memory, visuospatial, orientation, attention, language, executive function	Older adults	Yes	*NA*	No	Yes, >100 languages
BOMC [54]	To screen for cognitive impairment	6-item questionnaire Score range 0–28 points > 10: Signs of cognitive impairment or dementia	Memory, orientation, attention	Older adults	Yes	*NA*	No	Yes, <10 languages
CDT [55]	To screen for cognitive impairment	Multiple scoring methods and interpretations *Example:* *Freund scoring system; 7-point scoring scale* *≤ 4:Cognitive impairment*	Visuospatial, executive function	Older adults	Yes	*NA (*)*	Yes [58,59]	Translation not required
Mini-Cog [57]	To discriminate between persons with or without dementia in a community sample of culturally, linguistically, and educationally heterogeneous older adults	CDT + 3-item recall	Memory, visuospatial, executive function	Older adults	Yes	*NA*	No	Yes, <50 languages

Abbreviations: MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; BOMC, Blessed Orientation-Memory-Concentration Test; CDT, Clock-drawing test; NA, Not applicable given the initial validation population.
[*] Validation in cancer patients for the Freund scoring system [58,59].

attributable to cancer and/or treatment side effects [65]. Depression in older adults is associated with functional impairment, cognitive impairment, and an increased risk of dementia [66]. It is also associated with worse survival [67–69].

Several instruments, mainly PRO tools, were discussed for use among older adults with cancer, and some are also recommended to screen for depressive symptoms or depression in this population [23,49,50,70] (Table 3). Among these, the Center for Epidemiologic Studies Depression Scale (CES-D) [71], the GDS-15 [9] and the Hospital Anxiety and Depression Scale (HADS) [72] were validated in older adults with cancer [73]. While the Profile of Mood States - Short Form (POMS-SF) was not validated in older patients with cancer, its parent version, the Profile of Mood States, was. The CES-D and HADS are the most commonly used instruments in patients with cancer to assess the prevalence of depression [64].

While the CES-D was developed for research, the GDS-15 and HADS were initially developed for use in clinical settings. Compared to the other tools, the HADS has the main advantage of being developed for use in patients presenting with chronic diseases and thus avoids items that often confound the determination of psychiatric problems among the medically ill. Indeed, some questions of the CES-D or the GDS-15 could be inappropriate or inaccurate for older adults with cancer [73].

Revised cut-offs for detecting minor depression in older adults with cancer are available for these three instruments [73]. While MCIDs were determined for the GDS-15 and the HADS, MCID was only established for the short form of the CES-D (CESD-15) [74–76]. However, none of them were determined in older adults with cancer. Even though the CES-D presents the best specificity and sensitivity for detecting major depression in older adults with cancer, none of CES—D, GDS-15, and HADS were evaluated as satisfactory to detect minor depression in this population [73]. Considering these elements, these tools should be used carefully among older adults with cancer and future research is needed to develop an adequate tool for use in this population.

Other instruments are available to identify the presence of depressive disorders, such as the Beck Depression Inventory - Second version (BDI-II) [77], the Brief Symptom Inventory-18 (BSI-18) [78], the Patient Health Questionnaire-9 (PHQ-9) [79], the POMS-SF [80], or the Zung Self-Rated Depression Scale (Zung SDS) [81]. However, to the best of our knowledge, these instruments have not been validated yet in older adults with cancer.

Table 3
Depression assessment tools.

Tool name	Aim	Description and score interpretation	Initial population	Validated in			Available in several languages
				Older adults	Patients with cancer	Older adults with cancer	
CES-D [71]	To measure current level of depressive symptomatology, with emphasis on the affective component, depressed mood	20-item questionnaire comprising six scales reflecting major facets of depression: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance Score range: 0–60 Score ≥ 16: risk for clinical depression	General population	Yes	Yes	Yes [73]	Yes, >50 languages
GDS-15 [9]	To assess depression in geriatric populations	15-item questionnaire Dichotomously coded (yes/no) questions resulting in an overall depression severity scale Score range: 0–15 Score ≥ 5: Presence of depression	Older adults	Yes	*NA*	Yes [73]	Yes, <50 languages
HADS [72]	To detect states of anxiety and depression	14-item questionnaire: 7-item in the anxiety subscale (HADS-A), 7-item in the depression subscale (HADS-D) Score range: 0–42 Score ≥ 8: Presence of depression	Outpatients with chronic disease	Yes	Yes	Yes [73]	Yes, >100 languages
BDI-II [77]	To detect depression in normal populations or to assess symptom severity in clinical populations	21-item questionnaire Score range: 0–63 Score > 20: Depression Higher score = greater depressive symptoms severity	General population and psychiatric outpatients	Yes	Yes	No	Yes, >50 languages
BSI-18 [78]	To measure psychological distress and psychiatric disorders	18-item questionnaire Three domains: somatization, depression, anxiety Score range: 0–72 Higher score = greater distress and psychiatric disorders	General population and medical patients	Yes	Yes	No	Yes, <10 languages
PHQ-9 [79]	To detect depression and assess severity	9-item questionnaire 9 DSM-IV criteria Score range: 0–27 2–4 criteria rated as "more than half the days": depression 5+ criteria rated as "more than half the days": major depression	Primary care and obstetric-gynecology patients	Yes	Yes	No	Yes, >50 languages
POMS-SF [80]	To measure psychological distress	37-item questionnaire Six domains: anger, confusion, depression, vigor, fatigue, and tension Score range: −24-124 or 0–148 Higher score = higher mood disturbance	Patients with cancer	*NA*	Yes	No*	Yes, >50 languages
Zung SDS [81]	To identify the presence of depressive disorders in adults	20-item Index score range: 25–100 Index score ≥ 50: depressive disorder	General population	Yes	Yes	No	Yes, but unknown number of translations

Abbreviations: CES—D, Center for Epidemiologic Studies Depression Scale; GDS-15, Geriatric Depression Scale - 15-item; HADS, Hospital Anxiety and Depression Scale; BDI-II, Beck Depression Inventory - Second version; BSI-18, Brief Symptom Inventory-18; PHQ-9, Patient Health Questionnaire-9; POMS-SF, Profile of Mood States - Short Form; Zung SDS, Zung Self-Rated Depression Scale; NA, Not applicable given the initial validation population.

* Not validated in older adults, but the parent instrument (POMS) was [70].

4.4. Nutrition

Older adults experience higher rates of undernutrition and present higher risk of malnutrition than the general population [82]. Malnutrition is common in older adults with cancer, its prevalence ranging from 15% to 70%, and may be related to aging, the disease, and/or the cancer treatment [83,84]. In addition, malnutrition in older adults with cancer is associated with adverse clinical outcomes such as morbidity, mortality, decreased HRQoL, and treatment toxicities [85,86]. The evaluation of malnutrition can easily be performed by calculating the Body Mass Index (BMI) or assessing cachexia defined through an international consensus [87]. However, these performance measures are only based on weight measurements and may not be reliable in patients with cancer [88]. Thus, several instruments were developed to assess nutritional risk and were recommended for use in patients with cancer by the European Society for Clinical Nutrition and Metabolism (ESPEN) [89], while others were recommended by the SIOG [50]. These instruments are mainly care provider-reported but include patient-reported information. (Table 4).

The Patient-Generated Subjective Global Assessment - Short Form

Table 4
Nutrition assessment tools.

Tool name	Aim	Description and score interpretation	Initial population	Validated in			Available in several languages
				Older adults	Patients with cancer	Older adults with cancer	
CASCO [98]	To stage cachectic patients with cancer	5-component score: body weight loss and composition, inflammation/metabolic disturbances/immunosuppression, physical performance, anorexia, and quality of life Score range: 0–100 Score 15–28: mild cachexia Score 29–46: moderate cachexia Score 47–100: severe cachexia	Patients with cancer	*NA*	Yes	No	*N/A*
PG-SGA SF [90]	To assess the nutritional status	4-part questionnaire: weight, food intake, symptoms, activities and function Score range: 0–35 Higher score = greater risk of malnutrition Score 0–1: well-nourished Score: 2–8: at risk of malnourishment, moderately malnourished Score ≥ 9: severely malnourished, critical need for nutrition intervention and symptom management	Patients with cancer	*NA*	Yes	No	Yes, <50 languages
MNA [91]	To identify the elderly at risk of malnutrition and guide optimal nutritional intervention	18 item questionnaire 4 rubrics: anthropometric assessment, general assessment, short dietary assessment, subjective assessment Score range: 0–30 Score ≥ 24: well-nourished Score 17–23.5: risk of malnutrition Score < 17: malnourished	Older adults	Yes	*NA*	Yes [93,94]	Yes, <50 languages
DETERMINE [99]	To detect nutritional risk in older adults	10-item checklist Score range: 0–21 Score 0–2: Good Score 3–5: Moderate nutritional risk Score ≥ 6: High nutritional risk	Older adults	Yes	*NA*	No	*N/A*
SNAQ [100]	To early detect hospital malnutrition	3-item questionnaire related to weight loss, loss of appetite, and use of nutritional supplements and/or tube feeding Score range: 0–5 Score = 2: moderate malnutrition Score ≥ 3: severe malnutrition	Hospitalized patients	No*	Yes	No	Yes, <10 languages
MST [101]	To screen for malnutrition	4-item questionnaire on on appetite, food intake, and recent weight loss Score range: 1–5 Score ≥ 2: action needed	Hospitalized patients	Yes	Yes	No	Yes, <50 languages
NRS 2002 [102]	To identify malnourished hospitalized patients	4 pre-screening questions If one answered yes: impairment of nutritional status (percentage of weight loss, general condition, BMI, and recent food intake), disease severity (stress metabolism), age Score range: 0–7 Total score ≥ 3: nutritional risk	Hospitalized patients	Yes	No	No	Yes, but unknown number of translations
MUST [103]	To identify patients at nutritional risk, and to predict their clinical outcome	4-component instrument: unintentional weight loss, BMI, and food intake (acute disease-related effect inducing a phase of >5 days with no food intake) Score range: 0–8 Score ≥ 2: nutritional risk	Adults	Yes	Yes	No	Yes, <10 languages

Abbreviations: CASCO, Cachexia SCOre; PG-SGA SF, Patient-Generated Subjective Global Assessment - Short Form; MNA, Mini Nutritional Assessment; DETERMINE, DETERMINE Nutritional Index; SNAQ, Short Nutritional Assessment Questionnaire; MST, Malnutrition Screening Tool; NRS 2002, Nutritional Risk Screening 2002; MUST, Malnutrition Universal Screening Tool; NA, Not applicable given the initial validation population; N/A, Information not available.

* Specific tools developed for older adults: SNAQ65+: for patients in the community who are aged 65 and over, SNAQRC for the older adults in care homes or residential care.

(PG-SGA SF) [90], initially developed for patients with cancer, and the Mini Nutritional Assessment (MNA) [91], initially developed for older adults, are the most widely used in oncology [92]. They are both correlated with objective measures including anthropometric and laboratory tests for the assessment of malnutrition, and the MNA was validated in older adults with cancer [93,94]. An MCID was determined for both instruments enabling their use to measure change in nutritional status. Both scales are able to correctly classify patients as malnourished, although a lack of specificity in the MNA is worth mentioning [95]. However, a recent review highlighted that a screening tool that distinguishes between malnutrition, cachexia, and sarcopenia in older adults with cancer is needed [96]. The Global Leadership Initiative on Malnutrition (GLIM) criteria based on unintentional weight loss, low BMI, reduced muscle mass, reduced food intake, and disease burden were recently reported as an effective tool for nutrition assessment in the older adults with cancer, but further validation studies are needed [97].

Although they have not been validated yet in older adults with cancer, other tools are available to screen malnutrition, such as the Cachexia SCOre (CASCO) [98], the DETERMINE Nutritional Index [99], the Short Nutritional Assessment Questionnaire (SNAQ) [100], the Malnutrition Screening Tool (MST) [101], the Nutritional Risk Screening 2002 (NRS 2002) [102], and the Malnutrition Universal Screening Tool (MUST) [103].

4.5. Health-Related Quality of Life

HRQoL is a multidimensional construct that covers the subjective perceptions of the positive and negative aspects of the symptoms of patients with cancer, including physical, emotional, social, and cognitive functions as well as disease symptoms and side effects of treatment [104]. HRQoL is thus of major concern for patients with cancer and even more so for older patients for whom HRQoL may be more important than length of life [105,106]. The majority of patients with cancer would decide to undergo a treatment prolonging life but not compromising their HRQoL, and older adults with cancer prioritize HRQoL over length of life even more in their treatment decisions [105,107]. In addition, several studies have reported on the association between HRQoL and survival [108].

The consideration of HRQoL as a primary or co-primary outcome in RCTs dedicated to older adults with cancer is recommended by SIOG, the Alliance for Clinical Trials in Oncology, and EORTC and several instruments are available [17,109] (Table 5).

The EORTC QLQ-C30 [6] and the Functional Assessment of Cancer Therapy - General (FACT-G) [110] were both developed in the 1990s to assess HRQoL in patients with cancer in a research setting. The items of the QLQ-C30 questionnaire are organized into five functioning scales (physical, role, emotional, social, and cognitive functioning), eight symptom scales (fatigue, pain, nausea/vomiting, etc.), and one overall global health status/QoL scale. As for the FACT-G questionnaire, items are grouped into four HRQoL domains (physical, social/family, emotional, and functional well-being). These PRO tools can be supplemented by disease-, symptom-, and population-specific questionnaires (modules), and general questionnaires can also be used without the core questionnaire. For instance, a module specific to older adults can be used in addition to the EORTC QLQ-C30 core questionnaire (QLQ-ELD14) [111], and specific core questionnaires are available for palliative care settings for both the EORTC-QLQ and FACT questionnaires. These core questionnaires and/or the specific modules are the most widely used in oncology [112–114] as well as in geriatric oncology [115,116].

As a multidimensional outcome, several options are available to measure and quantify HRQoL depending on the outcome of interest (i.e., a specific domain of HRQoL) or a measure of self-reported global/QoL status.

If one is interested in one specific domain of HRQoL as a trial

Table 5
Health-related quality of life assessment tools.

Tool name	Aim	Description and score interpretation	QoL domains	Initial population	Validated in			Available in several languages
					Older adults	Patients with cancer	Older adults with cancer	
FACT-G [110]	To assess the health-related quality of life in cancer patients	27-item questionnaire Score range: 0–108 Higher score = better HRQoL	Physical, social/family, emotional, functional	Patients with cancer	*NA*	Yes	Yes [122]	Yes, >50 languages
QLQ-C30 [6]	To assess the health-related quality of life in cancer patients	30-item questionnaire Score range: 0–100 Higher score = better HRQoL	Global health, physical, social, emotional, cognitive, role, symptom-specific	Patients with cancer	*NA*	Yes	No (*)	Yes, >100 languages
SF-36 [125]	To measure functional health and well-being	36-item questionnaire Score range: 0–100 Higher score = better HRQoL	General health, physical, social, cognitive, role-physical, role-emotional, bodily pain, vitality	General population with chronic diseases	Yes	Yes	No	Yes, >100 languages
EQ-5D-5L [126]	To describe and value health	5-item questionnaire and one visual analogue scale Score range: 0–100 Higher score = better HRQoL	Mobility, self-care, usual activities, pain/discomfort, anxiety/depression	General population	Yes	Yes	No	Yes, >100 languages
WHOQOL-BREF [127]	To assess quality of life	26-item questionnaire Score range: 0–100 Higher score = better HRQoL	Physical, psychological, social, environment	General population	Yes	Yes	No	Yes, <50 languages
PROMIS-GH [128]	To assess health related quality of life	10-item questionnaire Score range: Higher score = better HRQoL	Overall, physical, emotional, social, pain, fatigue	General population	Yes	No	No	Yes, <50 languages

Abbreviations: HRQoL, Health-related quality of life; FACT-G, Functional Assessment of Cancer Therapy – General; QLQ-C30, Quality of Life Questionnaire Core 30; SF-36, Medical Outcomes Study Short Form 36, EQ-5D-5L, 5-Level European Quality of Life 5 Dimension; WHOQOL-BREF, World Health Organization Quality of Life-BREF; PROMIS-GH, Patient-Reported Outcome Measurement Information System - Global Health; NA, Not applicable given the initial validation population.

* A validated module specific to older adults can be used in addition to the EORTC QLQ-C30 core questionnaire (QLQ-ELD14) [111].

outcome (e.g., physical or cognitive functioning), one can thus rely on the relevant subscale of either questionnaire, just as others tools described in the previous sections to address these domains. MCID or minimal important difference (MID) were defined and validated for the total core questionnaires and for each subscale [110,117–120].

If self-reported global health/QoL status is of primary interest, then the dedicated QLQ-C30 global health/QoL status 2-item subscale can serve as primary endpoint. A disadvantage of this very brief two-item overall quality of life scale is that it may have less measurement precision than is desired for detecting group differences over time. In addition, it may not be a conceptually appropriate summary of the QLQ-C30, which contains a relatively large number of symptom scales and items. Although not addressing the same concept, an overall score taking all items into account can thus be computed for either the QLQ-C30 [121] or the FACT-G [120] questionnaires. Both of these summary scores were shown to be robust (i.e., good validity and responsiveness), and as such can avoid problems with potential type I errors that arise because of multiple testing when making comparisons based on the multiple outcomes generated by the questionnaires. This may reduce sample size requirements for HRQoL studies using the HRQoL questionnaire when an overall summary score is a relevant primary outcome.

As they were specifically developed for use in oncological research and validated in older adults with cancer [111,122], the QLQ-C30/ELD14 and FACT-G are highly relevant for assessing HRQoL in this population. One should, however, ensure that these PRO questionnaires are indeed self-completed by the patient, as HRQoL scores may tend to be higher when interviewer administered [123]. Luckett et al. proposed an informative decision tree for choosing between QLQ-C30 and FACT-G [124].

Although the QLQ-C30 and the FACT-G are the most widely used in oncology and geriatric oncology, other instruments are available to assess HRQoL, such as the Medical Outcomes Study Short Form 36 (SF-36) [125], the 5-Level European Quality of Life 5 Dimension (EQ-5D-5L) [126], the World Health Organization Quality of Life-BREF (WHOQOL-BREF) [127], and the Patient-Reported Outcome Measurement Information System - Global Health (PROMIS-GH) [128]. In addition, a novel functional instrument, the Elderly Functional Index (ELFI), was recently developed using items from the QLQ-C30 (9 items) and QLQ-ELD14 (3 items) and used as primary outcome in a recent trial [129,130].

4.6. Patients' Symptoms and Satisfaction

There is a growing interest in considering patients' experience and satisfaction as part of a large tolerability assessment [131]. Risk assessment is essential in RCTs evaluating treatment benefit and efforts are ongoing in order to modernize adverse event (AE) assessment and reporting [132]. This assessment is usually based on the report of toxicities during the trial and mainly performed by physicians reporting adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE defines adverse events and provides a grading scale for the severity of each one. However, compared to clinicians, patients may report more symptomatic toxicities [133,134] and clinicians underreport both the prevalence and severity of patients' symptoms [135]. In addition, PROs better reflect daily health status and are associated with better/improved HRQoL status [134–136]. Thus, the international societies and regulatory authorities recommend the inclusion of symptom PROs in clinical trials in order to assess disease-related symptoms and symptomatic adverse events. Those, however, are intended to complement, not replace, safety data. Recommendations were also published for a core symptom set recommended to be assessed across oncology trials where a PRO is measured, which includes 12 symptoms, specifically fatigue, insomnia, pain, anorexia (appetite loss), dyspnea, cognitive problems, anxiety (includes worry), nausea, depression (includes sadness), sensory neuropathy, constipation, and diarrhea [137]. In order to bring the patient perspective into toxicity reporting, a PRO version of the CTCAE was developed to complement the initial CTCAE [138,139]. PRO-CTCAE has demonstrated positive psychometric properties including construct validity, reliability, and responsiveness. Patients score separately the different aspects of a symptomatic adverse event, such as the presence, frequency, severity and/or activity interference associated with each term. Thus, PRO-CTCAE scores do not correspond to clinician CTCAE grades. This difference permits the analysis of patient-reported interference separate from severity, which may lead to insights for tolerability. Other tools, such as the M.D. Anderson Symptom Inventory [140] or the Edmonton Symptom Assessment [141] also aim to collect toxicity experienced by the patients themselves. While these tools were validated for patients with cancer, none of them were validated for older adults with cancer. However, the PRO-CTCAE was recently used in a large RCT in older adults with cancer and results were reported on the association between severe adverse events and treatment-related hospitalization and survival [142].

Finally, a summary measure of the overall side effect impact informing on the tolerability of a treatment is recommended by regulatory authorities [20]. Because individual patients may weigh some side effects as more important than others, a single global impression of severity item might be particularly relevant and will also lessen patient burden by reducing the number of items to complete. This issue can be addressed using a single question (e.g., “Please choose the response below that best describes the severity of your overall side effects from treatment over the past week,” where 0 represents none and 3 represents severe) or through dedicated items from existing PRO instruments (e.g., QLQ-C30 or FACT-G core questionnaires and/or modules).

Considering that pain is one of the most common symptoms in patients with cancer and associated with functional decline, depression, and HRQoL, it is an important issue in older patients with cancer [143–145]. Pain is the result of a complex process involving neurophysiological and psychological mechanisms leading to difficulties in assessing it. A five-step approach including self-report assessment, pathology consideration, behaviors assessment, caregiver input, and analgesic trial was recently recommended [146]. Regarding self-reported assessment, there are different tools to measure pain in patients with cancer as visual analog scales, verbal rating scales, numeric rating scales, and questionnaires [147]. As highlighted for older adults in general, there are a number of validated and reliable tools for use in older adults and the choice of tool should be based on the patient's ability to use the tool [148]. Again, dedicated items are available in the QLQ-C30 and FACT-G core questionnaires and/or modules.

In addition to the assessment of toxicities and pain, tools are also available to assess treatment satisfaction and decisional regret, such as the Cancer Therapy Satisfaction questionnaire, [149] measuring the individual's satisfaction with treatment (expectations of benefits and side effects), and the Decisional Regret scale, [150] measuring regret after health care decision. These tools are not yet validated in older adults with cancer, but similar questionnaires have been used in trials dedicated to older patients with cancer [151]. The patient perception of a treatment's benefit weighed against its harms may also be captured by asking the patient “Was the treatment worth it” (WIWI). Initially developed to evaluate patient perceptions of the value of clinical trial participation [152], WIWI was then used in cancer trials to assess worthwhileness of the cancer treatment and shown to be strongly associated with treatment duration, the reason for ending treatment, and HRQoL and less strongly with treatment efficacy (e.g., disease response) or toxicity (e.g., AE) [153]. Similarly, in the MRC FOCUS2 trial for older adult and frail patients, the concept of overall treatment utility (OTU) was introduced to reflect whether, from the viewpoint of both patient and clinician and with use of both objective and subjective measures, the treatment has been worthwhile [154]. While WIWI and OTU do not directly pertain to specific geriatric domains, they may inform on clinical practice, oncology research, and value frameworks.

5. Statistical Analyses, Clinical Trial Protocol, and Reporting

Several guidance documents reporting on statistical analyses, protocol contents, and reporting have been produced and are discussed in this section. Although these guidelines focused on PRO, they may also be relevant for patient-related outcome measures as well as performance measures and deserve to be addressed here.

5.1. Statistical Analyses

The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium (SISAQOL) was formed to establish PRO analysis recommendations [155]. Four issues were prioritized by the consortium: developing a taxonomy of research objectives that can be matched with appropriate statistical methods, identifying appropriate statistical methods for PRO analysis, standardizing statistical terminology related to missing data, and determining appropriate ways to manage missing data. The selection process for an appropriate PRO tool should thus be accompanied by a careful statistical methodology in order to guarantee unbiased interpretation of PRO-based trial results.

5.2. Study Protocol and Reporting

The SPIRIT guideline (Standard Protocol Items: Recommendations for Interventional Trials) provides the minimum content of a clinical trial protocol [156]. As the quality of PRO content in many protocols had been reported to be suboptimal regardless of the degree of adherence to SPIRIT [157,158], the SPIRIT-PRO, an extension of the SPIRIT 2013 statement, was developed to address this issue [159]. Although this guidance has been developed for trials for which PROs are primary or key secondary outcomes, researchers are encouraged to consider use of this guidance in all trials or clinical research studies in which PROs are collected, including if PROs are exploratory endpoints.

Similarly, a PRO extension to the CONSORT (Consolidated Standards of Reporting Trials) statement is available for reporting RCTs with PROs as primary or secondary outcomes [160], as these are often inadequately reported [161]. Presentation of PRO data in standalone articles, which may be published months or years after the main trial report, can be a barrier to patient reported outcome data uptake. Therefore, the CONSORT-PRO statement recommends that authors report primary or important secondary outcome for PRO results in their primary publication, according to the published CONSORT-PRO items.

6. Discussion

Over the past years, international societies and regulatory authorities have advocated for including PROs and patient-related outcomes when assessing treatment benefit in RCT including older adults with cancer. Recent systematic reviews have highlighted that there is still a lack of consideration for these outcomes in cancer RCTs, even those dedicated to older adults. The aim of the present report was to provide guidance for the selection of geriatric domains, PROs, and patient-related tools, and as such to promote their use in RCTs dedicated to older patients with cancer.

We identified the following domains as being of particular interest when assessing treatment benefit in older adults with cancer: functional autonomy, nutritional status, cognition, and depression. In addition, HRQoL, patients' symptoms, and satisfaction were also considered relevant to assess. We provided an extensive review of available PRO and patient-related outcomes tools, within each domain, and discussed their strengths and limitations based on published evidence.

We highlighted that some domains may be investigated through various tools. On the other hand, additional research is needed for other domains where further development and/or validation is warranted among older adults with cancer. Our review also illustrates the need for future studies to determine the MCID for tools to be able to measure differences over time or between groups, but for which no data are yet available. Moreover, when the MCID had been defined for a cancer population or a population of older patients, none has been defined specifically for older adults with cancer. Thus, MCIDs have to be validated in this population, for example by reanalyzing existing data. Finally, it is also worth mentioning that serious issues have been raised regarding incomplete reporting in the literature on MID, which thus threaten the optimal use of MID estimates to inform on the magnitude of effects on outcomes [162].

Another important issue is the burden on patients related to the multiplicity of tools and questionnaires that may be required to complete when participating in an RCT. Selection of PRO and patient-related outcomes should be carefully considered to minimize patient burden and improve the quality of data collected by focusing on the most meaningful and measurable outcomes, especially since several tools may overlap. The input of patient representatives to determine what is meaningful and relevant might be particularly valuable at the stage of trial design. More generally, obtaining stakeholder input in future iterations of the present initiative should also be considered in the future, as patient participation may impact outcome domain selection in core outcome sets for research [163].

Health literacy and education should also be considered when assessing PRO and/or patient-related outcomes. A study evaluating the readability of 45 PRO measures reported that nearly three-quarters of them required a grade level higher than 6 [164]. Thus, the interpretation of PRO scores must not pass over patients' literacy and education. This is even more true for instruments dedicated to cognition, such as MMSE/MoCA.

Finally, one cannot ignore that costs and copyrights may play a role when selecting a tool. This issue is well illustrated with the MMSE, for which copyright was enforced in 2000, leading to its gradual disappearance from clinical tool kits and textbooks [165]. Fortunately, several tools remain available for use free or charge and/or license. Considering this, we provided a table presenting cost and copyright rules for each tool discussed in this article (see Supplementary Material).

Interestingly, while their focus was on clinical practice, experts of the SIOG consensus statement on geriatric assessment in older patients with cancer concluded that several tools were available to evaluate geriatric domains, but the superiority of one tool over another had not been proven [50]. Similarly, in the context of clinical research, it is not possible to make recommendations on which PRO/tool to select for a given domain given the strengths and limitations of the various PROs/tools considered. Moreover, the literature on this topic might be elevated by conducting future systematic reviews for each geriatric domain. This paper thus provides an overview of PRO and patient-related outcome tools, to guide researchers when conducting clinical trials in older adults with cancer. One must carefully consider both the objective of the RCT (target population, site of the disease, treatment) and the characteristics of the PRO/tool (primary aim, validation studies, MCID, resources) to guide the choice of the most appropriate tool.

7. Conclusion

The aim of the report was to guide the researchers and clinicians involved in RCTs dedicated to older adults with cancer and relying on patient-related outcomes, including PROs. We reviewed the pros and cons of different available tools for multiple domains: functional autonomy, cognition, depression, nutrition, self-reported global/QoL status, as well as patients' symptoms and satisfaction. These considerations, together with the research objective of the trial, its target population, and the investigated interventions should thus drive the selection of the most relevant tools that will best address the research question.

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Author Contributions

Conception and Design: AG, PS, SMP, CB.
Data Collection: AG, CB.
Analysis and Interpretation of Data: all authors.
Manuscript Writing: AG, CB.
Approval of Final Article: all authors.

Declaration of Competing Interest

PS: Member of advisory boards: BMS, EISAI. EB: Receipt of travel supports: Pfizer, Sandoz; Receipt of honoraria: Eli Lilly, Pfizer, Seagen; Receipt of consultation fees: Daiichi, Pfizer, Sandoz.

KLC: Consultancy: Roche; Research funding: AstraZeneca.

EB: Consultancy: Daiichi, Menarini, Pfizer, Sandoz; Honoraria: Pfizer, Eli Lilly, Incyte, Seagen; Travel support: Gilead, Pfizer, AstraZeneca, Novartis; Board member: Daiichi.

RK: Consultancy: MSD, Astellas, BMS, J&J, Eisai, Ipsen, Merck; Honoraria: MSD, BMS, Eisai, Ipsen, Merck, J&J; Travel support: AstraZeneca, Ipsen.

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Appendix A. Supplementary Data

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