

# Patient-reported outcome (PRO) measurements in chronic and malignant diseases: Ten years' experience with PRO-algorithm-based patient-clinician interaction (telePRO) in AmbuFlex

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**Research Article**

**Keywords:** Algorithm, Chronic disease, Decision support systems, Malignant diseases, Outpatient follow-up, Patient-reported outcome measures, Questionnaires

**Posted Date:** March 30th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1458851/v1>

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## **Patient-reported outcome (PRO) measurements in chronic and malignant diseases: Ten years' experience with PRO-algorithm-based patient-clinician interaction (telePRO) in AmbuFlex**

Running title: Ten years' experience with telePRO

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## Abstract

### **Background**

Patient-reported Outcome (PRO) measures may be used as the basis for out-patient follow-up. Instead of fixed appointments, patients attend follow-up based on disease-specific questionnaires filled in at home (telePRO). The questionnaire is handled in real time by a disease-specific algorithm, which assigns an outcome color reflecting clinical need. Questionnaires and algorithms are constructed in a consensus process with clinicians. We aimed to describe AmbuFlex' telePRO solutions and the algorithm outcomes and variation, to discuss differences between patient groups, and to highlight possible applications and challenges.

### **Methods**

TelePRO solutions with more than 100 processed questionnaires were included in the analysis. Data were retrieved together with data from national registers.

### **Results**

From 2011 to 2021, 29 disease-specific telePRO solutions were implemented within 24 different ICD-10 groups. A total of 42,015 patients were referred and answered 171,268 questionnaires. An existing disease-specific instrument with cut-off values was available for four solutions, whereas items were selected or developed ad hoc for the other solutions. Mean age ranged from 10.7 years to 73.3 years. Mortality varied between 0 and 528 per 1000 patient years. Variations in algorithm outcomes reflected differences in patient groups and aims while different solutions within the same patient group varied little.

### **Discussion**

TelePRO can be applied in diseases where PRO can be used to evaluate clinical status and needs. Questionnaires and algorithms should be adapted for the specific patient groups and clinical aims.

## Key words

Algorithm, Chronic disease, Decision support systems, Malignant diseases, Outpatient follow-up,  
Patient-reported outcome measures, Questionnaires

## Background

### *PRO at group and patient level*

The term Patient-reported Outcome (PRO) was coined by the US Federal Drug Agency to standardize the use of such data to support labeling claims in medical product development [1]. Interest in using PRO data, also at the individual patient level, is growing [2-4]. PRO data are usually used during the consultation as a tool to support communication, and research has shown possible benefits in terms of process measures such as improved patient-clinician communication and better detection of problems [5-8]. However, when patients fill in PRO data at a distance, e.g. at home, PRO data can be processed before the consultation, providing information that may enhance flexibility in care and more efficient use of health care services without compromising quality of care [3, 9-11] and some cases even improve Quality of Life and survival [12-14].

### *Development of telePRO*

Patients with chronic and malignant diseases have variable need of clinical attention. If they attend standardized out-patient follow-up, they may not need attention on the day of a fixed appointments, resulting in waste of transport to hospital, patient time, and clinician time. Paradoxically, the waiting area may be flooded with patients on the day of an unnecessary consultation, making it impossible for a patient with an actual need of attention to get an appointment. In telePRO, PRO constitutes the basis for the contact and fixed appointments are replaced with fixed disease-specific questionnaires as the basis for follow-up. The questionnaire is filled in at home, and an appointment is made only if the questionnaire indicates a need or a patient wish of a consultation. TelePRO may also be used for other purposes, enhancing flexibility (see below). Based on an existing system for PRO data collection for group level use [15, 16], we developed the telePRO system AmbuFlex [17]. The aim was four-fold: first, to improve quality of care by flagging important symptoms and produce better documentation for the patient record; second, to promote patient-centered care with focus on patients' needs and knowledge about own disease; third, to optimize the use of resources in the healthcare system, and finally, to use

the PRO data in research and hospital quality assurance [17]. AmbuFlex, Center for Patient-reported Outcomes, is a part of the public hospital organization in Region Central Denmark where we since 2011 have developed and implement telePRO solutions in chronic and malignant diseases, also in other parts of Denmark. The development is a teamwork with 27 employees including coordinators with a health professional background, software developers, quality assurance specialists, and health researchers. Apart from algorithm-based solutions, AmbuFlex has also implemented clinical PRO in the traditional way, where PRO is used solely to promote communication and consultation quality.

### *Use of telePRO*

Algorithm-based PRO solutions consist of three elements: the PRO data collection, the PRO-based algorithm, and the presentation of the PRO measures in a graphical overview [17]. The technology for the elements is generic, but configurable for disease-specific solutions with different aims, e.g., screening for symptom deterioration and need type of contact and as a treatment decision tool. In a solution with the main purpose to screen for the patients' need of contact a green, yellow, or red outcome color is used based on a "red flag" approach. A red outcome reflects a need of clinical attention. However, the patients are allowed to overrule the PRO-based algorithm by indicating a wish for contact. The principle of AmbuFlex is further explained in Figures 1 and 2. The development of the questionnaires and algorithms is described elsewhere [17]. The aim of this paper was (1) to describe all AmbuFlex's diagnosis-specific telePRO solutions, (2) to describe the algorithm outcomes and variation in outcomes, (3) to discuss similarities and differences between patient groups, and (4) to highlight possibilities and challenges in the use of telePRO.

## Material and methods

### *Selection of solutions*

Included in the analysis were AmbuFlex solutions developed for research or routine use using algorithms if more than 100 processed questionnaires were available. Solutions in same patient groups using similar questionnaires and algorithms were merged before analysis.

### *Data collection*

Questionnaire data and the results of the algorithms were retrieved from the internal database together with information on the patient's sex, age, and vital status, last updated January 15, 2022. Information on vital status is automatically retrieved online by the AmbuFlex system from the Danish civil registration system [18]. Mortality was calculated with person-years measured from the date of response to the patient's first questionnaire to the date of death or the date of the last vitality status update. Observation time in AmbuFlex was calculated as the time span between the dates of the first and the last answered questionnaire. Information on algorithm outcome is recorded in the AmbuFlex system for each questionnaire with the outcome colors green, yellow, or red. A questionnaire has a red outcome if just one item in the algorithm is flagged red, while a green outcome is applied if all flags have green codes. All other questionnaires contain a yellow algorithm outcome. Since the algorithms are solution-specific, the meaning and consequence of the outcome colors differ between solutions.

### *Data analysis*

Descriptive tables were constructed using AmbuFlex's own software [15]. Algorithm outcomes were anonymized and transferred for further analysis into the R statistical software package [19]. The ranking of the three algorithm outcome colors is the same for all solutions (red is more severe than yellow, which is more severe than green). In most solutions, the difference in consequences between a yellow and a red algorithm outcome is smaller than the difference between a green and a yellow outcome. For example, in some solutions, green outcomes are handled automatically by the AmbuFlex software, while yellow and red outcomes are reviewed and evaluated by a clinician. In some solutions only two colors were applied (green/red or yellow/red). To allow

comparison across solutions, severity grade values of 0, 2, and 3 were assigned to green, yellow, and red outcomes and used to rank the questionnaires from each patient (Table 1). Each questionnaire can have one of three outcome colors, and therefore a patient with at least three answered questionnaires may have one of seven combinations of algorithm outcomes (severity group). Graphs were constructed for each solution depicting the frequency and variation in algorithm outcomes. Before plotting, patients were sorted by severity group. The total area of each color represents the overall proportion of that algorithm outcome, while the within-group variation is represented for each severity group. Components of variation in algorithm outcome severity score (within- and between-patient) were calculated for solutions with more than one answer from each patient. The `anovaVCR` function in the R VCR package was used to calculate components of variations in unbalanced designs [19, 20]. The square root of variation was used for tables and plots to maintain interpretable values (severity grade).

## Results

A total of 29 disease-specific solutions were included covering 42,015 referred patients from 89 hospital departments all over Denmark. As one department may refer patients to more than one solution, the number of unique departments was lower. Also, the same patient may be referred to more than one solution, e.g., cancer patients may attend different solutions at different disease stages, one during active treatment and another during follow-up. Furthermore, patients may have several diseases corresponding to different solutions. There were 41,144 unique patients, 871 of whom had attended more than a single solution, and 16 had been referred to three solutions.

### *Algorithm aims*

The aims the algorithms may be divided into four groups, shown by examples in Table 2 and tabulated for each solution in Table 3. The first aim, need of clinical attention (“Need”), represents the original purpose of AmbuFlex, namely PRO-based out-patient follow-up, where PRO, not

hospital visits, form the basis for the contact. In some solutions mild cases are handled automatically, and a new questionnaire is scheduled after a patient-specific assigned interval (e.g., 3 months) (n = 7 solutions, Table 3), while in 14 solutions questionnaires with green outcomes are also reviewed. The second aim ("Path," n = 3 solutions) uses telePRO to select the most relevant type of clinical path, e.g., a telephone or in-clinic consultation with a doctor or a nurse. The third aim ("Treatment", n = 2 solutions) uses telePRO to decide if, e.g., planned antineoplastic treatment should be postponed. Frequently, side effects incompatible with a treatment are not discovered before the patient shows up for treatment, wasting expensive prepared medicine. The aim "Instruction" uses algorithms to generate patient-specific on-screen messages with instructions to the patient based on the PRO. This is implemented in three disease groups: bladder cancer [21, 22], immune therapy for malignant melanoma [23], and screening for depression in patients with ischemic heart diseases [24]. TelePRO was implemented in a broad range of conditions including nearly all ICD-10 main groups, the highest number of solutions being in malignant (n = 8) and neurological diseases (n = 7) (Table 3). The most diverse use was in malignant diseases, which apart from out-patient follow-up also applied telePRO during active treatment (IT and M3, Tables 2 and 3) and to detect disease progression (PW). AmbuFlex is also used among cancer inpatients and patients attending palliative care, although without use of algorithms.

### *Patients*

The mean age of the referred patients was 57.2 years (SD 16.0 years) and 41.3% were women. The patient populations differed on nearly all parameters between the solutions (Table 4). The youngest patients were found in solutions for pain in children (SK) (10.6 years) and the oldest in chronic kidney disease (N2) (73.3 years). With respect to mortality, the range was from 0 to 528 per 1000 patient years in patients with endometriosis (EN) and patients with lung cancer (PW), respectively. The patients submitted 171,268 questionnaires during a total observation time of 68,094 years. The longest follow-up time was in patients with epilepsy and sleep disorders, with a median follow-up of 4.3 and 4.0 years. The longest observation time (26,918 years, Table 4) was in sleep disorder (SA). The median number of questionnaires from each patient ranged from a single questionnaire to 86 in patients with COPD (KO). In lung cancer (PW), 55% of questionnaires came

from patients delivering 50 or more responses (Table 5), while the same was the case for 96% in COPD (KO). At the beginning of the period, most responses were collected by paper questionnaires, up to 92% in the patients with knee arthrosis, which ran from 2011 to 2013, while in the current solutions nearly all patients are contacted by secure e-mail and the questionnaires are answered online. This significant development in our PRO data collection is described elsewhere [16].

### *The algorithms*

The algorithms were unique for each solution because they are based on disease-specific questionnaires [17, 25-27]. Examples of algorithms and meaning of color codes are shown in Table 2 and Supplemental Table 1. In four solutions, the core of the algorithm was based on group-validated questionnaires with fixed threshold values (Table 3). In the remaining solutions, no relevant instruments or threshold score values were available, and the algorithms were constructed as series of single items or scales, each addressing a clinical issue. We used SF-36 [28], SCL-90 [29] and the EORTC Item Library to select single items [30]. If an item could not be located, the item was created ad hoc, typically with response categories adapted from EORTC ("Not at all/A little/Quite a bit/Very much"). Questions regarding general health were collected from SF-36 [28]. At least one question regarding general health was asked in 19 (66%) of the solutions. All three colors were used in 23 solutions, green and red in 5, and yellow and red in 1 solution (Table 4).

### *Algorithm outcomes*

The algorithm outcomes for each solution are listed in Table 6. The content and purpose of the algorithms were heterogenic. Accordingly, the proportion of green outcomes varied between 1% and 59%. A graphical "fingerprint" of algorithm outcomes and intra-group variation is displayed in Figure 3 for each solution. The total area of each color represents the proportion of that outcome. The within-group variation may be read vertically for each severity group. Some solutions were dominated by one algorithm outcome, e.g., breast cancer (AB) and ischemic heart disease (AK). No

or little intra-patient variance (AK, DP) was seen if there was only a single questionnaire for each patient or the patient had recently been referred. In lung cancer (PW), more than 95% of the responses came from patients with variation in algorithm outcomes. Different solutions within the same patient group have similar “fingerprints” although questionnaires and algorithms differed (Table 3). In prostate cancer (P2/P3 and PC), the solutions had a similar distribution of outcomes and a similar pattern within severity groups. The most important difference was a larger proportion of patients with all-red algorithm outcomes in PC, which may reflect referral of more patients with advanced disease. The variation in outcomes (severity grade, defined in Table 1) is described in Table 6 and Figure 4. The largest variation in severity was found in lung cancer (PW) and the lowest in the proxy solution in epilepsy (EP). After breaking down the total variation in within- and between-patient variation, the highest within-patient variation was 50% (bladder cancer, B3), while the lowest variation was 29% in patients with multiple sclerosis (SC).

## Discussion

During the last 10 years, telePRO has been applied in 29 disease-specific versions of AmbuFlex in 24 different patient groups in Denmark. The analyses patients and questionnaires showed large variations in virtually all parameters, reflecting that diagnosis-specific solutions are unique with respect to questionnaire content, algorithms, clinical purpose, and patient characteristics. A common denominator is that the solutions were developed using the same methods and are supported by the AmbuFlex platform.

### *The four different aims of telePRO*

Aim “Need”, where telePRO is used to evaluate the patient’s need for clinical attention, was used in the majority of the implementations (Table 2). Denis et al. evaluated weekly symptom reported by patients with lung cancer [12]. Twelve symptom items automatically triggered an alert to the clinicians if a pre-defined threshold was exceeded. A similar set-up was described in a study by Basch et al. [13]. In this study, patients could weekly self-report side effect symptoms after

chemotherapy, and e-mail alerts were sent to clinicians if symptom scores worsened by a pre-defined threshold. Armstrong et al. described use of remote PRO with a mobile app during the first 30 days following ambulatory breast reconstruction [11]. Patients reported pain on a visual analog scale and quality of recovery on a 9-item questionnaire daily for 2 weeks and thereafter weekly for 2 weeks. Clinicians were alerted to red flags, and abnormally high pain scores or low quality of recovery scores prompted in-person follow-up. Brundage et al. summarize experiences [31] and point out that if PRO data are used remotely between visits, it is important to use predefined threshold levels. Decisions regarding the definition of these thresholds must be made by experts with sufficient expertise to weigh the implications of false-positive versus false-negative alerts [32]. In AmbuFlex, clinical experts are involved in defining the PRO-based algorithm thresholds and decide whether a specific response category should be given a green, yellow, or red color. In solutions where green outcomes are handled automatically ("Need<sup>auto</sup>", Tables 2 and 3), the risk of false negative cases is more important than that of false positive cases and a high sensitivity should be a key consideration. Regarding the aim "Instruction," the telePRO algorithm generates an instruction to the patient instead of an alert to the clinician, which basically poses the same demands of sensitivity. PRO-based alerts in the "eRAPID" system [33] include PRO data about adverse events related to chemotherapy treatment. The system provides tailored feedback to patients if they report any severe symptoms. In the case of less severe symptoms, the patients are asked to follow self-management advice. If a serious problem is reported the patients are advised to contact the hospital as soon as possible. Thus, alerts based on PRO data can be tailored not only to clinicians but also to patients. As pointed out by Brundage et al., considerations regarding defining clinical alerts and threshold levels should be based on when, how, and to whom alerts are directed and whether PRO data are combined in the algorithm with other important data, e.g., a blood test or data from the patients' medical record, [31]. In the two aim types ("Path" and "Treatment"), all questionnaires are individually evaluated and therefore the consequences of false negatives are less severe.

#### *Differences between the solutions*

Outcome patterns, like differences between patients, were very different (Figures 3 and 4). Lung cancer (PW) and COPD (KO) had the largest variation in algorithm outcomes, with nearly three times more variation than did Epilepsy Proxy (EP), and Obesity (FF). This is corroborated by the contrast in variation in severity scores (Table 6 and Figure 4). No gold standard for variation exists, but except for screening purposes with just one measurement, there must be considerable variation over time; otherwise, you only need to ask the patient once and such a setting is not relevant for telePRO.

### *Limitations*

Out-patient groups are the main target for telePRO-based follow-up, but not all diseases and patients are suitable. For a disease to be relevant, evaluation of the patient's state must rely on measures reportable as PRO, which may also include self-measurements. PRO-based follow-up should not be a "one-size-fits-all". Each patient should be evaluated before referral and allowed to return to standard follow-up whenever he or she wishes to do so. This is for ethical reasons, but is also a way to monitor and evaluate the telePRO solution. PRO-based follow-up requires a mentally capable patient. However, in patient groups with mentally disabled persons, proxy versions of the questionnaire may be applied. We did this in the pain in children (SM) and patients with epilepsy (EP) solutions in 231 referred patients compared to 6,222 in the main solution (AE) [17].

### *Questionnaires and algorithms*

Traditionally, validated questionnaires are validated for purposes other than telePRO, where the main question in aim "Need" may be expressed as: "Does this patient need clinical attention at the moment?", in aim "Path": "Which type of clinical contact is most relevant?", in aim "Treatment": "Is this patient ready for the planned treatment?", and in aim "Instruction": "What is the most relevant instruction to the patient?". We based the solution solely on a traditionally validated questionnaire and cut-off values in screening for depression [34], hip and knee alloplastic operations [35, 36], and rheumatoid arthritis [37]. In all other solutions, algorithms were based on

series of single items adapted from item libraries or developed together with clinicians [38]. When using the single-item approach, each item is provided its own cut-off value and a sum-score is not available, making it possible for clinicians to achieve consensus regarding items, cut-off values, and hence the whole algorithm. This process runs in parallel with revisions of the questionnaire and takes years to mature. The first epilepsy solution (AE) was launched in 2011 and has subsequently been revised four times. After 5 years without any changes, a national revision is now in progress.

### *Length of questionnaires*

Doctors and nurses will often focus on the length of the questionnaire as a critical factor and on the clinical relevance of each item. From our experience, patients are more concerned with the last issue than the first. Patients accept long questionnaires if they find the questions relevant. Questionnaires in research-initiated solutions are longer (Table 3), which may be accepted by the participating patient because they volunteered to participate, while several of the clinical solutions have become standard care and the patient has to explicitly opt out. A good reason for clinicians to prefer short questionnaires is that both patient and clinicians will expect action to be taken if the patient reports a problem. Examples are depressive symptoms or sexual problems in solutions in specialized departments, some clinicians expecting such issues to be handled by the family doctor. There is no simple solution to this problem. In some cases, explicit guidelines have been developed [39, 40].

### *TelePRO vs PRO for consultation support*

In most AmbuFlex telePRO solutions, PRO is also used as a tool to enhance the consultation process. During the last decade, an increase in the use of PRO at the patient level has been seen in clinical care. However, PRO has no value in itself; it is the context and actual use that makes the difference. If PRO is an add-on to existing clinical practice, the implementation is very dependent on the commitment of the individual clinicians and in some implementations only a minor part of

responses are ever seen by a clinician [16, 41]. In telePRO based follow-up, PRO constitutes the basis itself for the follow-up. Each time a questionnaire is received, it is either handled automatically (green response) or put on an alert list, like incoming lab tests, where it remains until a clinician has reviewed it and decided whether the patient should be contacted or not. Therefore, virtually all questionnaires are used: automatically, as a decision tool, and/or as a basis for patient-clinician interaction in the consultation.

### *Ethical considerations*

In AmbuFlex, some answers from patients (green algorithm outcomes) are handled automatically by AmbuFlex' software ("Need<sup>auto</sup>"), while yellow and red outcomes are reviewed by clinicians. Subsequent action is then planned based on the PRO overview, the actual and previous answers and other information in the electronic health record. In outpatient follow-up, patients are instructed to contact the department, emergency room, or their family doctor in event of sudden health deterioration between appointments. This solves a potential hazard for PRO-based follow-up if a questionnaire is lost for some reason. In most solutions, non-responding patients are appointed a specific code on the alert list. Also, only patients capable of evaluating and reporting their own health should be referred.

### *Administrative challenges*

Questionnaires with a calculation of scores or a color code for decision aid are considered medical devices if collected electronically and used in the treatment of patients. As such, PRO solutions must ensure patient safety and be compliant with EU legislation for Medical Device Regulatory (MDR). Patient safety is a cornerstone, also within the application of PRO in clinical practice. The questionnaire and color code must uncover the defined aim and be understandable and meaningful to patients and clinicians, and the IT system must be reliable and secured. There are standards for the development and test of IT systems, but it is still unclear how best to develop and validate questionnaires and color codes. As outpatients are instructed to contact their family

doctor or the department directly if their disease worsens, it makes little sense to treat PRO solutions according to the same rules as hospital medical electronic equipment.

### *The patient perspective*

Two of the aims of AmbuFlex are to optimize the use of resources and to promote patient-centered care. Is there a contradiction between the patient's interests and the interests of clinicians and hospital owners? Generally, we would say no. In AmbuFlex's very first years, health administrators and hospital owners in Denmark sometimes considered AmbuFlex as an easy way to cancel appointments for patients with no or little need of clinical attention, but did not acknowledge the resources needed to implement and run it. Fortunately, this view has changed, and telePRO is now merely seen as a tool for achieving better quality of care. Few patients are interested in consultations when there is no need. However, clinicians also need to see less complicated cases to be able to experience the whole spectrum of a disease; otherwise, they will develop a biased picture of prognosis.

### Conclusion

TelePRO can be applied in any setting where PRO can be used to evaluate patient clinical status and needs. Questionnaires and algorithms should be adapted for specific patient groups and clinical aims.

### Acknowledgements

Edwin Stanton Spencer, M.D. is acknowledged for skillful assistance in preparing the final version of the manuscript.

**Table 1.** Grouping of telePRO outcomes by severity based on algorithm outcome colors in all questionnaires from each patient

Green <sup>1</sup> Severity grade 0	Algorithm outcome color		Severity group
	Yellow Severity grade 2	Red <sup>2</sup> Severity grade 3	
1+	0	0	0
1+	1+	0	1
1+	0	1+	1.5
1+	1+	1+	1.7
0	1+	0	2
0	1+	1+	2.5
0	0	1+	3

Note: Green, yellow, and red algorithm outcomes were assigned the severity grade values of 0, 2, and 3 to and reflect that the difference in consequences between a green and a yellow algorithm outcome is larger than the difference between yellow and red in all solutions. Each questionnaire can have one of three algorithm outcome colors, and hence patients with at least three answered questionnaires may have one of seven combinations of algorithm outcomes that define the patient's severity group.

1: All items in algorithm with green color codes

2: At least one item with red color code

**Table 2.** Examples of aims of algorithm use in AmbuFlex telePRO solutions

Solution ICD10 group (solution ID)	Description and aim	Algorithm outcome		
		Green <sup>1</sup>	Yellow	Red <sup>2</sup>
<b>Aim "Need": Need of clinical attention (automated cancellation)</b>				
C34 (PW) Lung cancer [25, 42]	Patients are referred after a CT scan showing non-progressive diseases and answer PRO once a week to detect progression.	No contact. Automatic scheduling of next questionnaire.	n/a	Possible disease progression. A clinician reviews PRO and EHR data and decides if need for earlier imaging.
G40 (AE) Epilepsy [17, 38, 43-45]	Patients answer PRO every 3, 6, 12, or 24 months. The purpose is to identify patients who need contact with the outpatient clinic.	No contact. Automatic scheduling of next questionnaire.	Possible need of contact. PRO and EHR data are reviewed. In 62% no further contact.	Definite need of contact, e.g., episodes of seizures or planning of pregnancy.
<b>Aim "Need": Need of clinical attention (decision support)</b>				
E10 (DM) Type-1 DM [46, 47]	Patients answer PRO 2 weeks prior to preplanned consultation. The purpose is to identify and cancel unnecessary consultations.	No obvious need of contact. 75% canceled without further contact.	Possible need of contact. 49% canceled without further contact.	Definite need of contact. No consultations were canceled.
N18 (N2) Chronic kidney disease [26, 48]	Patients answer PRO every 3rd month. PRO and laboratory tests inform clinicians whether the patient needs contact with the outpatient clinic.	No obvious need of contact. In 83%, no further contact before the next questionnaire.	Possible need of contact and a clinician may call the patient. In 44%, no further contact.	Definite need of contact. A clinician calls the patient or schedules a face-to-face consultation.
<b>Aim "Path": Selection of relevant type of clinical contact (telephone/clinic or nurse/doctor)</b>				
C50 (AB) Breast cancer	Patients attending follow-up answer PRO, which is used to evaluate need of consultation and indicate relevant clinician.	Letter to the patient including medication for the next period.	Telephone consultation with nurse.	A doctor reviews PRO and EHR and decides further action.
<b>Aim "Treatment": Treatment preparation</b>				
C80 (IT/IN) Cancer NOS	Patients treated with immune therapy answer PRO 2 days before treatment. PRO is used together with blood test and EHR data for treatment adjustment.	Treatment is ordered.	Treatment is ordered. A clinician decides whether further action is necessary.	Treatment not ordered. A clinician contacts the patient and decides further plan.
<b>Aim "Instruction": Instructions or advice to the patient</b>				
C 67 (B3) Bladder cancer [21, 22]	Patients receiving chemo- or immunotherapy answer PRO with alert algorithm with on-screen pop-up instructions to the patient.	No action.	Advice to encourage self-treatment with supportive care advice.	Advice to contact the department to obtain advice or hospitalized for the given treatment.
I20 (AK) Ischemic heart disease [24]	Patients with atherosclerotic heart disease, cardiomyopathy, or heart failure answered PRO 4 weeks after discharge.	Postal letter with test result. No further action.	n/a	Postal letter to patient with test result and advice to contact family doctor.

1: All items with green color codes

2: At least one item with red color code

EHR: Electronic Health Record, NOS: Not otherwise specified

**Table 3.** Characteristics of questionnaires and algorithms used in AmbuFlex telePRO 2011–2021

ICD10 group (solution ID)	Solution	Questionnaire			Algorithm		
	In operation	Content <sup>1</sup>	Items	Aim <sup>2</sup>	Items <sup>3</sup>	Patient override <sup>4</sup>	Color codes <sup>5</sup>
B20 HIV disease (HV) ##	2015->	[1,3]	43	Path	32 items	M	GYR
C34 Lung cancer (PW) #	2018->	EORTC [49] [2]	17	Need <sup>auto</sup>	12 items, f:1	M	GR
C43 Malignant melanoma (IM) #	2017-19		70	Instruction	24 items		GR
C50 Breast cancer (AB)	2016->	EORTC CTCAE [50][2]	72	Need+Path	69 items	Q & M	GYR
C61 Prostate cancer (PC)	2014-19	EORTC [1]	73	Need	50 items, f:7	Q	GYR
C61 Prostate cancer (P2/P3)	2018->	EORTC [2]	45	Need	38 items, f:2	Q & M	GYR
C67 Bladder cancer (B3) #	2019->21	CTCAE [2]	101	Instruction	37 items		GYR
C80 Cancer NOS (M3/KN)	2015->		60	Treatment	57 items, f:2	M	GYR
C80 Cancer NOS (IT/IN)	2019->		50	Treatment	47 items, f:1	M	GYR
E10 Type-1 DM (DM) ##	2017->	PAID [51] WHO5 [52] [1]	34	Need	28 items, f:2	Q & M	GYR
E66 Obesity (FF)	2021->	[1]	18	Need	16 items, f:1	M	GYR
G35 Multiple sclerosis (SC)	2016->	HAQ [53] WHO5 [1,3]	52	Need	39 items, f:1	Q & M	GYR
G40 Epilepsy (AE/E3) ##	2012->	WHO5 [1,3]	47	Need <sup>auto</sup>	38 items., f:2	Q & M	GYR
G40 Epilepsy (EP) (proxy)	2015->		34	Need	27 items, f:1	Q & M	YR
G47 Sleep disorders (SN)	2013->	ESS [54] [1,3]	64	Need	49 items, f:3	Q & M	GYR
G47 Sleep disorders (SA)	2014->	ESS [1,3]	50	Need <sup>auto</sup>	34 items, f:1	Q & M	GYR
G47 Sleep disorders (NV)	2017->	ESS, WHO5 [1,3]	48	Need <sup>auto</sup>	36 items, f:2	Q & M	GYR
G91 Hydrocephalus (HC)	2017->	WHO5	59	Need+Path	51 items, f:1	Q & M	GYR
I20 Ischemic heart ds. (AK)	2011-17	HADS [34]	14	Instruction	0 items, f:2		GR
J44 COPD (KO)	2015->		13	Need <sup>auto</sup>	11 items, f:2	M	GYR
J45 Asthma (AT/A5)	2015->	ACQ [55]	8	Need	8 items, f:3	Q & M	GYR
K50 Crohn's disease (IB/I2)	2017->	WHO5 [1,3]	49	Need	46 items., f:5	Q & M	GYR
M05 Rheumatoid arthritis (RA/LG) #	2014->	Flare [37]	40	Need	4 items, f:4	Q	GYR
M10 Gout (AU)	2020->		30	Need	28 items, f:1	Q & M	GYR
M16 Arthrosis, hip (DP) #	2011-13	Oxford Hip [36] [1]	14	Need <sup>auto</sup>	0 items, f:1		GR
M17 Arthrosis, knee (DP) #	2011-13	Oxford Knee [35] [1]	14	Need <sup>auto</sup>	0 items, f:1		GR
N18 Chronic kidney ds. (N2) ##	2018->	EQ5D [56] [1,3]	63	Need	27 items	Q	GYR
N80 Endometriosis (EN)	2020->	WHO5 [1]	45	Need	35 items, f:1	Q & M	GYR
R52 Pain NOS (SM) (proxy)	2018->		18	Need	10 items, f:9	M	GYR

1: All solutions included one or more ad-hoc questions or single items from instruments. General health items: [1] SF-36 GH1 [28], [2] EORTC QLQ C29 [49], [3] SF-36 HT [28].

2: Clinical purpose of algorithm. Need: need of clinical attention (auto: automatic cancellations), Path: selection of relevant clinical path for contact, Treatment: treatment preparation, Instruction: instruction of the patient (cf. Table 2)

3: Number of items included in the algorithm. f: function depending on a combination of items

4: The patient may override the algorithm by answering a specific question (Q) or enter any text into a text message field (M), which will induce both a red or yellow algorithm outcome.

5: Outcome colors used by the algorithm (cf. Fig 1)

#: Research initiated

##: Research enriched

**Table 4.** Characteristics of patients referred to AmbuFlex telePRO 2011-2021

ICD10 group (solution ID)	Departments	Patients	Age (SD)	Gender	Mortality	Follow-up (yrs)	Observation
B20 HIV disease (HV)	1	568	48.2 (12.3)	29.4	8	2.6 (5.9)	1,082
C34 Lung cancer (PW)	8	230	67.2 (7.8)	60.0	528	0.4 (2.9)	154
C43 Malignant melanoma (IM)	1	72	62.4 (11.9)	52.8	158	0.4 (0.6)	23
C50 Breast cancer (AB)	1	1,552	63.4 (11.7)	99.1	19	1.9 (4.9)	1,801
C61 Prostate cancer (PC)	5	1,273	65.1 (6.5)	0.0	7	0.7 (2.4)	838
C61 Prostate cancer (P2/P3)	5	2,102	68.7 (8.0)	0.0	29	0.5 (3.0)	1,089
C67 Bladder cancer (B3)	4	119	67.8 (9.0)	23.9	313	0.3 (0.7)	34
C80 Cancer NOS (M3/KN)	3	3,917	63.1 (11.9)	62.3	131	0.4 (6.5)	3,128
C80 Cancer NOS (IT/IN)	2	977	66.5 (10.6)	40.6	258	0.4 (2.0)	427
E10 Type-1 DM (DM)	1	290	47.1 (14.1)	47.6	5	2.7 (4.6)	706
E66 Obesity (FF)	1	60	43.2 (9.8)	76.7	0	0.1 (0.5)	5
G35 Multiple sclerosis (SC)	2	109	62.1 (9.0)	63.3	34	2.3 (3.7)	140
G40 Epilepsy (AE/E3)	3	6,222	47.5 (18.9)	50.5	19	3.6 (9.8)	21,979
G40 Epilepsy (EP) (proxy)	4	231	43.5 (18.0)	44.2	31	2.5 (6.7)	508
G47 Sleep disorders (SN)	2	160	32.8 (11.9)	56.9	1	4.0 (7.8)	551
G47 Sleep disorders (SA)	6	12,188	56.3 (12.2)	26.3	7	2.9 (7.3)	26,917
G47 Sleep disorders (NV)	1	640	61.8 (11.5)	20.6	18	2.1 (4.4)	935
G91 Hydrocephalus (HC)	1	230	42.7 (18.4)	51.3	13	1.7 (4.2)	352
I20 Ischemic heart ds. (AK)	2	5,000	66.2 (12.5)	40.6	38	0.0 (0.0)	0
J44 COPD (KO)	2	77	69.9 (8.5)	49.4	155	1.7 (6.3)	167
J45 Asthma (AT/A5)	4	228	48.8 (14.5)	61.4	0	0.9 (3.8)	245
K50 Crohn's disease (IB/I2)	6	3,203	46.3 (15.5)	55.5	2	1.5 (4.8)	4,564
M05 Rheumatoid arthritis(RA/LG)	5	1,178	62.5 (12.9)	69.8	14	1.5 (7.3)	2,061
M10 Gout (AU)	1	72	60.2 (14.5)	13.9	19	0.2 (1.1)	15
M16 Arthrosis, hip (DP)	6	330	67.8 (10.9)	61.5	18	0.2 (1.1)	112
M17 Arthrosis, knee (DP)	7	475	67.3 (9.0)	57.7	15	0.2 (1.2)	152
N18 Chronic kidney ds. (N2)	3	45	73.3 (10.0)	33.3	29	1.2 (1.9)	54
N80 Endometriosis (EN)	1	116	35.9 (6.4)	100.0	0	1.0 (1.7)	46
R52 Pain NOS (SM) (proxy)	1	349	10.7 (3.1)	36.1	0	0.0 (2.2)	9

**Table 5.** telePRO questionnaires processed in AmbuFlex 2011-2021

ICD10 group (solution ID)	Questionnaires	Questionnaires per patient					Web <sup>1</sup>
	Total n	Median n	1 %	2–9 %	10–49 %	50+ %	%
B20 HIV disease (HV)	1,370	2	12	88	0	0	100
C34 Lung cancer (PW)	8,058	23	0	3	42	55	100
C43 Malignant melanoma (IM)	1,193	17	0	8	91	0	100
C50 Breast cancer (AB)	3,239	2	16	84	0	0	88
C61 Prostate cancer (PC)	2,500	2	6	131	0	0	86
C61 Prostate cancer (P2/P3)	5,050	2	10	90	0	0	93
C67 Bladder cancer (B3)	1,515	11	1	23	84	0	100
C80 Cancer NOS (M3/KN)	26,546	6	1	46	106	16	100
C80 Cancer NOS (IT/IN)	6,060	4	3	52	45	0	100
E10 Type-1 DM (DM)	2,183	8	1	71	28	0	100
E66 Obesity (FF)	102	1	33	67	0	0	100
G35 Multiple sclerosis (SC)	230	2	19	81	0	0	72
G40 Epilepsy (AE/E3)	28,608	4	3	92	5	0	68
G40 Epilepsy (EP) (proxy)	708	3	8	92	0	0	39
G47 Sleep disorders (SN)	941	6	2	76	23	0	83
G47 Sleep disorders (SA)	36,309	3	10	90	0	0	85
G47 Sleep disorders (NV)	1,532	2	14	86	0	0	89
G91 Hydrocephalus (HC)	859	3	5	92	3	0	100
I20 Ischemic heart ds. (AK)	5,000	1	100	0	0	0	20
J44 COPD (KO)	14,249	86	0	0	4	96	100
J45 Asthma (AT/A5)	1,121	3	3	66	31	0	100
K50 Crohn's disease (IB/I2)	17,422	3	3	48	49	0	100
M05 Rheumatoid arthritis (RA/LG)	4,136	2	6	85	21	0	89
M10 Gout (AU)	165	2	14	86	0	0	100
M16 Arthrosis, hip (DP)	332	1	100	0	0	0	16
M17 Arthrosis, knee (DP)	476	1	100	0	0	0	12
N18 Chronic kidney ds. (N2)	192	4	3	97	6	0	79
N80 Endometriosis (EN)	173	1	42	58	0	0	100
R52 Pain NOS (SM) (proxy)	999	2	10	89	1	0	100

1: Percentage of internet-based responses.

**Table 6.** Variation in algorithm outcome in AmbuFlex telePRO 2011-2021

ICD10 group (solution ID)	Algorithm outcome					Severity grade variation		
	Total n	Green %	Yellow %	Red %	Severity grade <sup>1</sup> Mean	Total	Within- patient %	Between- patient %
B20 HIV disease (HV)	1,370	13	58	30	2.0	0.90	35	65
C34 Lung cancer (PW)	8,058	59		41	1.2	1.48	40	60
C43 Malignant melanoma (IM)	1,193	17		83	2.5	1.14	48	52
C50 Breast cancer (AB)	3,239	4	69	27	2.2	0.62	46	54
C61 Prostate cancer (PC)	2,500	8	39	53	2.4	0.85	46	54
C61 Prostate cancer (P2/P3)	5,050	7	57	36	2.2	0.76	45	55
C67 Bladder cancer (B3)	1,515	16	10	74	2.4	1.10	50	50
C80 Cancer NOS (M3)	26,546	6	36	58	2.5	0.76	49	51
C80 Cancer NOS (IT/IN)	6,060	19	55	26	1.9	1.01	48	52
E10 Type 1 DM (DM)	2,183	4	33	63	2.6	0.69	36	64
E66 Obesity (FF)	102	2	97	1	2.0	0.37	45	55
G35 Multiple sclerosis (SC)	230	3	54	43	2.4	0.68	29	71
G40 Epilepsy (AE/E3)	28,608	18	63	20	1.8	0.94	42	58
G40 Epilepsy proxy (EP)	708		84	16	2.2	0.36	34	66
G47 Sleep disorders (SN)	941	1	66	33	2.3	0.53	33	67
G47 Sleep disorders (SA)	36,309	10	44	46	2.3	0.89	42	58
G47 Sleep disorders (NV)	1,532	6	36	58	2.5	0.80	47	53
G91 Hydrocephalus (HC)	859	10	51	39	2.2	0.87	43	57
J44 COPD (KO)	14,249	35	43	22	1.5	1.19	38	62
J45 Asthma (AT/A5)	1,121	12	10	78	2.5	1.01	36	64
K50 Crohn's disease (IB/I2)	17,422	8	62	30	2.1	0.77	43	57
M05 Rheumatoid arthritis (RA/LG)	4,136	27	54	19	1.6	1.07	46	54
M10 Gout (AU)	165	1	12	87	2.8	0.48	36	64
N18 Chronic kidney ds. (N2)	192	6	29	65	2.5	0.80	45	55
N80 Endometriosis (EN)	173	3	46	50	2.4	0.73	47	53
R52 Pain NOS (SM) (proxy)	999	52	39	8	1.0	1.12	41	59

Note: Solutions with only one questionnaire per patient are not included.

1: See Table 1

**Supplemental Table 1. Items in algorithms and color codes in three selected solutions.****Epilepsy (AE/A3)**

Item	Color codes				
Number of seizures during the last year	0	> 0			
Number of absence seizures during the last 3 months	0	> 0			
Number of generalized seizures during the last 3 months	0	> 0			
Seizure impairment	Yes	No			
Seizure injury	No	Yes, but not serious	Serious damage		
Emergency room visit due to epilepsy	Yes	No			
Relatives' worried	Never	Rarely	Occasionally	Frequently	Don't know
Headaches	Never	Occasionally	Sometimes	Often	Very often
Dizziness	Never	Occasionally	Sometimes	Often	Very often
Tremor/shaking	Never	Occasionally	Sometimes	Often	Very often
Double vision	Never	Occasionally	Sometimes	Often	Very often
Loss of appetite	Never	Occasionally	Sometimes	Often	Very often
Eating too much	Never	Occasionally	Sometimes	Often	Very often
Difficulty remembering	Never	Occasionally	Sometimes	Often	Very often
Difficulty concentrating	Never	Occasionally	Sometimes	Often	Very often
Aggression	Never	Occasionally	Sometimes	Often	Very often
Fatigue	Never	Occasionally	Sometimes	Often	Very often
Sadness	Never	Occasionally	Sometimes	Often	Very often
Fear of having seizures	Never	Occasionally	Sometimes	Often	Very often
Problems with sexuality	Never	Occasionally	Sometimes	Often	Very often
Being suicidal	Never	Occasionally	Sometimes	Often	Very often
Well-being WHO-5 Index	Score < 50 or just one extreme answer				
General health	Excellent	Very good	Good	Fair	Poor
General health compared to last year	Much better	Somewhat better	About the same	Somewhat worse	Much worse
Medication adherence	Daily	Weekly	Monthly	Never / very rarely	
Side effects	No	Yes, a few	Yes, some	Yes, many	
Work less because of epilepsy	Yes	Partly	No		
Social limitations	No	Yes			
Alcohol consumption	> consume 14/21 units a week				
Use of recreational drugs	Never	Monthly	Weekly	Daily	
Pregnant	Yes	No			
Planning pregnancy	Yes	No			
Car driving last month	Yes (+ seizures)	No			
Message to the clinic (free text)	Any topic				
What is your current need of contact with the outpatient clinic?	I will call the clinic if I need a contact	I would like a clinician to call me	I wish for an appointment in the clinic	I don't know	

**Lung cancer (PW)**

Item	Color codes						
	Very poor					Excellent	
How would you rate your overall health during the past week?	1	2	3	4	5	6	7
	Not at all	A little	Quite a bit	Very Much			
Were you short of breath?	1	2	3	4			
Have you had pain?	1	2	3	4			
Were you tired?	1	2	3	4			
Have you lacked appetite?	1	2	3	4			
How much did you cough?	1	2	3	4			
Did you cough up blood?	1	2	3	4			
Body temperature	≥38.2						
Hoarse voice worsened during the past week?	Yes						
Facial swelling worsened during the past week?	Yes						
Do you sense a growing tumor?	Yes						
How much do you weigh?	≥ 3 kg weight loss compared to first measure						
In the past week, have you had other symptoms that you think may be associated with your cancer? (Free text)						Any text	

**Chronic kidney disease (N2)**

Item	Color codes					
Lack of appetite	Not at all	Somewhat	Moderately	Very much	Extremely	
Aversion to food	Not at all	Somewhat	Moderately	Very much	Extremely	
Feeling of unease	Not at all	Somewhat	Moderately	Very much	Extremely	
Nausea	Not at all	Somewhat	Moderately	Very much	Extremely	
Vomiting	Not at all	Somewhat	Moderately	Very much	Extremely	
Itchy skin	Not at all	Somewhat	Moderately	Very much	Extremely	
Shortness of breath	Not at all	Somewhat	Moderately	Very much	Extremely	
Swollen legs	Not at all	Somewhat	Moderately	Very much	Extremely	
Dizziness	Not at all	Somewhat	Moderately	Very much	Extremely	
Difficulty remembering	Not at all	Somewhat	Moderately	Very much	Extremely	
Difficulty concentrating	Not at all	Somewhat	Moderately	Very much	Extremely	
Restless legs discomfort?	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
How much of the time did you feel tired?	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
How much physical pain have you had?	None	Very mild	Mild	Moderate	Severe	Very severe
Were you limited in doing regular daily activities?	Not at all	A little	Quite a bit	Very much		
Have you been constipated?	Not at all	A little	Quite a bit	Very much		
Have you had diarrhea?	Not at all	A little	Quite a bit	Very much		
Have you had to urinate frequently at night?	Not at all	A little	Quite a bit	Very much		
Have you had trouble sleeping at night?	Not at all	A little	Quite a bit	Very much		
Were you worried about your future health?	Not at all	A little	Quite a bit	Very much		
How often do you have difficulty remembering to take all your medication?	Daily	Weekly	Monthly	Never/Rarely		
In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor	
Compared to 1 year ago, how would you rate your health is general now?	Much better	Somewhat better	About the same	Somewhat worse	Much worse	
Do you experience other symptoms?	No	Yes, [Free text]				
Message to the clinic (free text)	Any text					
What is your current need of contact with the outpatient clinic?	I will call the clinic if I need a contact	I would like a clinician to call me	I wish for an appointment in the clinic	I don't know		

**Green** No need of contact with the outpatient clinic with respect to this item.

**Yellow** May need contact with respect to this item.

**Red** Need of contact with the clinic with respect to this item.

Note: For information regarding time reference and exact wording of questions and response categories, consult the individual papers.

## Figure legends

### Figure 1. Patient pathways in PRO-algorithm-based follow-up. Example: AmbuFlex/epilepsy.

Patients are individually referred by the patient's clinician. Patients complete a disease-specific telePRO at pre-defined individual intervals, e.g., 3 months. The system prompts patients to fill in the PRO through "e-Boks" (secure national e-mail platform). The epilepsy telePRO includes 47 items covering number of seizures, medicine adherence, symptoms, general health, and psychosocial function measured using the WHO-5, items from the SF-36, SCL-92 and ad-hoc developed items. An item covers the patient's wish of contact to ensure that patients always can get an appointment. As part of development, an expert group has marked the response categories in the telePRO with a green, yellow, or red color based on a "flag" approach. Red flag: need of clinical attention (e.g., planning pregnancy, seizure impairments, suicidal thoughts, or if the patient wishes contact). A green flag indicates no need of clinical attention, a yellow flag possible need of attention, and a red flag need of attention. "All-green" outcomes are managed automatically by the AmbuFlex system and a new telePRO is sent to the patient at the pre-defined interval, while red and yellow algorithm outcomes are reviewed by a clinician (Figure 2).

**Figure 2.** Screenshot of the clinician's PRO overview. Example: AmbuFlex/epilepsy

The telePRO responses are presented in a graphic overview inside the electronic health record (EHR) system. All red and yellow algorithms outcomes are shown to the clinicians on an alert list. For red outcomes, the clinicians contact the patient either by telephone or by an in-clinic appointment. For yellow outcomes, the clinicians evaluate the PRO data together with other available data and contacts the patient if necessary.

**Figure 3.** Distribution of PRO-algorithm outcomes

Along the X-axis in each figure, the algorithm outcomes are ordered patient-wise by their severity group (cf. Table 1), so that questionnaires from patients with the least severe outcomes (solely green algorithm outcomes) are on the left and questionnaires from patients with the most severe outcomes (solely red algorithm outcomes) are on the right. Y-axis: the cumulative percentage of algorithm outcome colors in each severity group. SQ: Singleton questionnaires, i.e., questionnaires originating from patients who so far have answered only one questionnaire and thus can possess no variation.

**Figure 4.** Standard deviation and components of variation (within- and between-patient) in algorithm outcome

Algorithm outcome for each questionnaire is measured as a discrete variable, severity grade, where green = 0, yellow = 2 and red = 3 (see Table 1)

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## Declarations

### *Funding*

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

### *Competing interests*

The authors have no relevant financial or non-financial interests to disclose.

### *Author contributions*

NHI contributed to the study conception, design, analysis and drafted the first version of the manuscript. All authors contributed to the design of the individual projects (solutions) described on the paper. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### *Ethics approval*

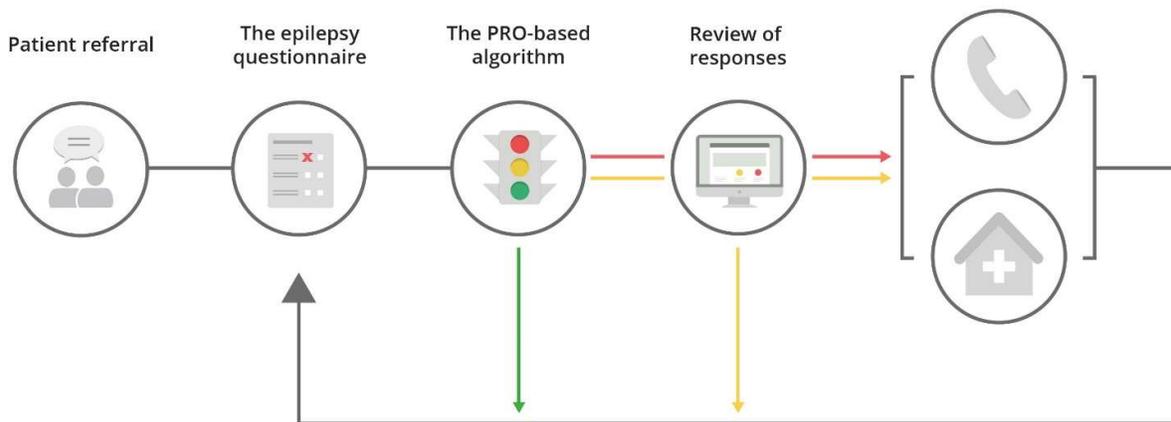
This study was performed in line with the principles of the Declaration of Helsinki. This is a meta-analysis. The Ethics Committee in Region Central Denmark has given approval to the included studies which required an approval and has confirmed that no ethical approval was required for the other studies.

### *Consent to participate*

This is a meta-analysis. No informed consent was needed.

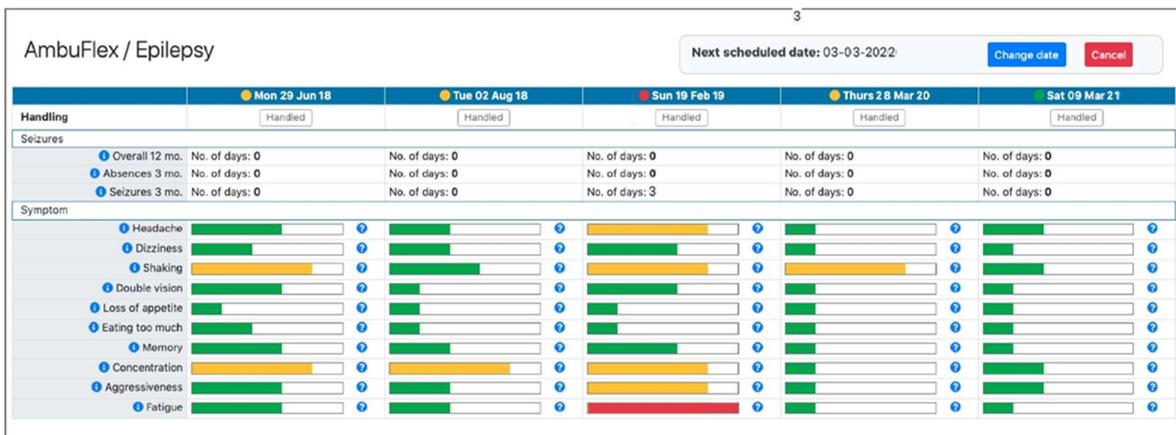
### *Consent to publish*

This is a meta-analysis. No informed consent to publish was needed.



**Figure 1.** Overview of the pathway of PRO-based follow-up. Example: epilepsy.

Patients are individually referred by the patient’s clinician. Patients complete a disease-specific telePRO at pre-defined individual intervals, e.g., 3 months. The system prompts patients to fill in the PRO through “e-Boks” (secure national e-mail platform). The epilepsy telePRO includes 47 items covering number of seizures, medicine adherence, symptoms, general health, and psychosocial function measured using the WHO-5, items from the SF-36, SCL-92 and ad-hoc developed items. An item covers the patient’s wish of contact to ensure that patients always can get an appointment. As part of development, an expert group has marked the response categories in the telePRO with a green, yellow, or red color based on a “flag” approach. Red flag: need of clinical attention (e.g., planning pregnancy, seizure impairments, suicidal thoughts, or if the patient wishes contact). A green flag indicates no need of clinical attention, a yellow flag possible need of attention, and a red flag need of attention. “All-green” outcomes are managed automatically by the AmbuFlex system and a new telePRO is sent to the patient at the pre-defined interval, while red and yellow algorithm outcomes are reviewed by a clinician (Figure 2).



**Figure 2.** Screenshot of the clinician’s PRO overview. Example: epilepsy.

The telePRO responses are presented in a graphic overview inside the electronic health record (EHR) system. All red and yellow algorithm outcomes are shown to the clinicians on an alert list. For red outcomes, the clinicians contact the patient either by telephone or by an in-clinic appointment. For yellow outcomes, the clinicians evaluate the PRO data together with other available data and contacts the patient if necessary.

