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Monitoring multidimensional aspects of quality of life after cancer immunotherapy: protocol for the international multi-centre, observational QUALITOP cohort study

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Monitoring multidimensional aspects of quality of life after cancer immunotherapy: protocol for the international multi-centre, observational QUALITOP cohort study

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ABSTRACT

Introduction: Immunotherapies, such as immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy, have significantly improved the clinical outcomes of various malignancies. However, they also cause immune-related adverse events (irAEs) that can be challenging to predict, prevent and treat. Although they likely interact with health-related quality of life (HRQoL), most existing evidence on this topic has come from clinical trials with eligibility criteria that may not accurately reflect real-world settings. The QUALITOP project will study HRQoL in relation to irAEs and its determinants in a real-world study of patients treated with immunotherapy.

Methods and analysis: This international, observational, multi-centre study includes consortia from France, the Netherlands, Portugal and Spain. It will include adult cancer patients treated with immunotherapy from historical real-world databases, medical administrative registries and specifically recruited prospective cohorts. Clinical health status, HRQoL and psychosocial well-being will be monitored until 18 months after treatment initiation with a tailored questionnaire completed at regular intervals. Using advanced statistical methods, including causal inference methods, artificial intelligence algorithms and simulation modelling, we will use data from the QUALITOP cohort to improve the understanding of the complex relationships between treatment regimens, patient characteristics, irAEs and HRQoL.

Ethics and dissemination: All aspects of the QUALITOP project will be conducted in accordance with the Declaration of Helsinki and with ethical approval from a suitable local ethics committee, and all patients will provide signed informed consent. In addition to standard dissemination efforts in the scientific literature, the data and outcomes will contribute to a smart digital platform and medical data lake. These will (1) help increase knowledge about the impact of immunotherapy, (2) facilitate improved interactions between patients, clinicians and the general population, and (3) contribute to personalised medicine.

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Keywords

Neoplasms, Immunotherapy, Quality of Life, Drug-related Side Effects and Adverse Reactions, Immune Check Point Inhibitors, Receptors, Chimeric Antigen

Strengths and limitations of this study

- The QUALITOP project will create an international, multi-centre, real-world cohort that aggregates data of multiple types and from multiple sources.
- The resulting agile data and analytics platform will improve the quality of data available to care professionals when interacting with patients, helping to bring personalised medicine to the forefront.
- By developing innovative analytic tools that respect European privacy regulations, the project will accelerate knowledge acquisition for the stakeholders.
- Despite its potential benefits, the QUALITOP project relies on data from diverse patient groups and from partly validated patient questionnaires.

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INTRODUCTION

Cancer immunotherapy has revolutionised oncology care over the last two decades, adding to the existing therapeutic arsenal through its unique action in stimulating the immune system to recognise and attack cancer cells.[1] Two subtypes of immune intervention that have gained particular interest, namely immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T cells (CAR T-cells), have hugely different mechanisms of action, indications and adverse events. Moreover, we lack long-term data on their health effects due to their relative novelty. International registries that monitor patient well-being in real-life settings provide invaluable opportunities to fill such knowledge gaps.

Immunotherapies trigger unique toxicities by activating the immune system to attack healthy cells. These immune-related adverse events (irAEs) occur in up to 96% of patients who receive ICIs, with severe irAEs reported in 10%–28% of patients receiving ICI monotherapy (Common Terminology Criteria for Adverse Events, grade ≥3) [2–5] and 59% of patients receiving combination therapy.[5] Dermatological, gastrointestinal and endocrine irAEs are most common, and management varies from symptomatic treatment for mild (grade 1–2) irAEs to corticosteroid or immunosuppressant (e.g., infliximab) treatment, or even permanent immunotherapy cessation, for life-threatening (grade 4) irAEs.[6] Nevertheless, toxicity profiles after ICI therapy appear more favourable than those of chemotherapy, with lower risks of developing any AEs or severe AEs (grade ≥3) for immunotherapy.[7] CAR T-cell therapy also causes various treatment-specific irAEs, with cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, infection and cytopenia the most common and severe in the acute phase (<28 days after CAR T-cell infusion).[8] Although irAEs can be life-threatening, they are usually reversible with early intervention. The most common long-term side effects are ongoing cytopenias, impaired immune reconstitution with B-cell aplasia, T-cell depletion and hypogammaglobulinemia with increased risk of infection.[9]

Besides improved clinical outcomes, immunotherapy should offer the patient psychosocial benefits

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compared with conventional therapies. To this end, trials have reported smaller impairments in health-related quality of life (HRQoL), longer times to HRQoL deterioration and better control of cancer symptoms.[10,11] However, immunotherapies and their associated irAEs may still affect HRQoL given that we know little of their associated late-onset and long-lasting effects.[12] Moreover, although Immunotherapy has clear and proven benefits over conventional anticancer treatments,[10,11,13–19] this evidence has predominantly come from clinical trials that have strict eligibility criteria. These data may exclude patients with poor performance status (Eastern Cooperative Oncology Group, performance status >1), concomitant cancers, auto-immune diseases or long-term systemic corticosteroid use.[3,20] Therefore, we do not know if the clinical and psychosocial benefits of immunotherapy in trial settings apply to real-world cohorts. The growth in survivor populations as these treatments elicit durable clinical responses and long-term remission for malignancies that previously had poor prognoses [21] emphasises the need for research into the long-term well-being and HRQoL of patients treated with these therapies.

We aim to study the multidimensional aspects of patients' HRQoL, the irAEs that develop during ICI and CAR T-cell therapy, and the relevant determinants of both, using a purpose-built smart digital platform with a medical data lake. This digital platform will improve data provision to various stake holders about risk profiles for irAE development or HRQoL deterioration. In this way, we can improve personalised and shared decision making for future patients eligible for immunotherapy.

METHODS AND ANALYSIS

Study design

The *'Monitoring multidimensional aspects of **Qua**lity of **Li**fe after cancer **I**mmuno**T**herapy, an **O**pen smart digital **P**latform for personalised prevention and patient management'* (QUALITOP) project is an international, multi-centre, real-world, observational cohort study. We will provide insights into

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the medical and psychosocial determinants of quality of life after cancer immunotherapy, making use of big data analyses, artificial intelligence and simulation modelling, before integrating the results in an information technology platform developed for the project. Additional information can be found on the project's website.[22]

We will study adverse events and quality of life among patients with cancer during and after immunotherapy. The QUALITOP cohort will combine a historical cohort of existing patients and a prospective cohort enrolled specifically for this project (**Figure 1**). The historical cohort will comprise patient data routinely collected in existing databases and medical registries in Spain, France, Portugal and the Netherlands, for which existing informed consent allows the re-use of data within the context of this European collaboration. For the prospective cohort, patients will be recruited in the same countries under the coordination of Hospital Clinic de Barcelona (IDIBAPS), Hospices Civils de Lyon, Instituto Português de Oncologia Lisboa, and Amsterdam University Medical Centers and University Medical Center Groningen, respectively. **Figure 2** shows the study timeline. Note that patients will not be included in both the historic and prospective cohorts.

Patient selection

Patients will be eligible for inclusion in a cohort if they are aged ≥18 years at the time of signing informed consent and have an oncological diagnosis either treated or to be treated with ICIs or CAR T-cells (as monotherapy or in combination with other anticancer treatments). Patients treated as part of a clinical trial may also be included if permitted by the clinical trial. However, we will exclude patients who are pregnant, under guardianship or who refuse to sign informed consent. For the prospective cohort, patients can be recruited from the decision for immunotherapy until their second cycle of immunotherapy. Patients receiving CAR T-cell therapy will be recruited from after leukapheresis to the start of lymphodepleting chemotherapy, before CAR T-cell infusion.

Study outcomes

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The primary outcome of the QUALITOP study is HRQoL, combining the patient's perspective of their physical, psychological and social functioning.[23] We will measure this outcome repeatedly in the prospective cohort and obtain data for a selection of patients and time points in the historic cohort. The secondary outcome of the QUALITOP study is the incidence and severity of irAEs, which we will extract from the electronic records for patients in both cohorts.

Data collection

Overview of data sources and timeline

Patient data for both the historic and prospective cohorts will come from existing and new databases at sites in France, the Netherlands, Portugal and Spain, as summarised in Table 1 and detailed in Supplemental File 1. Each study site has different specialisations and will cover different oncological diagnoses and therapies.

Table 1. Overview of data sources and their population characteristics per country

Study site	Name of existing study/database	Cohort + period of data collection	Oncological diagnosis	Therapy
France				
Hospices Civils de Lyon	Immucare Elderly	Historical (2007–2020)	Any solid tumour	ICIs
Hospices Civils de Lyon	Immucare BASE	Historical (2019 onward) Prospective (2021 onward)	Any solid tumour	ICIs
Hospices Civils de Lyon	QoLD CART	Historical (2021 onward)	Lymphoma	CAR T-cells
Hospices Civils de Lyon	QUALITOP CART	Prospective (2022 onward)	Lymphoma	CAR T-cells
The Netherlands				
University Medical Center Groningen	OncoLifeS	Historical (2015 onward) Prospective (2021 onward)	Lung cancer	ICIs
Nationwide CAR-T cohort	Follow that CAR	Historical (2020–2021) Prospective (2021 onward)	Lymphoma	CAR T-cells
Nationwide Cancer Registry (IKNL)	eQuiPe	Historical (2016–2020)	Any malignancy	Any treatment
Portugal				
Instituto Português de Oncologia, Lisboa	QUALITOP Lymphoma	Prospective (2021 onward)	Lymphoma	CAR T-cells, ICIs

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Spain				
Hospital Clinic de Barcelona (IDIBAPS)	Xarxa Melanoma	Historical (2020–2021) Prospective (2021 onward)	Melanoma	ICIs
Abbreviations: CAR, chimeric antigen receptor; ICIs, immune checkpoint inhibitors.				

Figure 2 shows the proposed timeline of patient monitoring in the historic and prospective cohorts. Data for eligible patients from the historic cohorts were collected between 2016 and 2021, while patient inclusion for the prospective cohorts was initiated in April 2021 and will continue until January 2023. Afterwards, inclusion is intended to be continued in a sustainability programme. We will monitor patients closely for the first 6 months of treatment or until cessation, after which patients will enter a phase of less intensive monitoring until 18 months after treatment initiation or the QUALITOP project ends (**Figure 2**). Clinical data will be extracted automatically from electronic patient files for both cohorts where possible, with manual extraction by project members for all other data. The QUALITOP questionnaire, which aims to collect data from various psychosocial domains, will only be used in the prospective cohort.

Data collection in the prospective cohort

Except in France, data from the prospective arm of the cohort are being collected and managed in REDCap (Research Electronic Data Capture), hosted by the participating institutions.[24,25] REDCap is a secure, web-based platform designed to support data capture for research studies. It provides the following: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. In France, data collection is being managed in Easily, a web-based electronic health record platform developed locally and hosted at Hospices Civils de Lyon. The database structure fits the common set of covariates in QUALITOP.

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Clinical data

Clinical data will be extracted from electronic patient files for each routine visit in the first 6 months of treatment and at fixed timepoints in the following year (9, 12 and 18 months). The timing of routine visits will differ by treatment type (ICI or CAR T-cell). We will assess medical history, medication use, prior anticancer treatments and cancer characteristics at the initiation of immunotherapy. Both at baseline and during follow-up, we will collect data from physical examinations (i.e., weight, performance status, blood pressure), laboratory assessments (i.e., C-reactive protein, neutrophils, leukocytes) and related to irAEs according to the Common Terminology Criteria for Adverse Events, version 5, of the National Cancer Institute.[26] Data about treatment for irAEs will be collected according to BioPortal's Drug Ontology,[27] available in REDCap. We will evaluate treatment response using the RECIST criteria for solid tumours [28] and the Lugano criteria for lymphomas.[29]

Psychosocial questionnaires

We developed psychosocial questionnaires to assess the multiple dimensions of quality of life and its potential psychosocial determinants in patients, necessary for the minimal data set of each patient included in the prospective cohort. A more in-depth questionnaire is issued at baseline and a shorter version is issued during follow-up at 3, 6, 12 and 18 months. We also modified the questionnaire slightly for patients receiving CAR T-cell therapy. **Table 2** summarises the domains included in each version of the questionnaire.

The flowchart in **Figure 3** illustrates the hypothesised framework for the interrelatedness of the questionnaire domains and their association with quality of life. We created French, English, Portuguese, Spanish and Dutch versions of the questionnaires, and when no validated translation existed, an external service provider specialising in academic and medical translation completed the translation. A researcher in each country also proofread the questionnaires, ensuring that the English version was consistent with his/her language.

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Table 2. QUALITOP questionnaire domains at baseline and during follow-up

Questionnaire domains	Source	Baseline	Follow-up (3, 6, 12, 18 months)
Part 1: Personal and work situation			
Sociodemographic factors (work, education, family and living situation)	Ad hoc items	x	*
Gender roles	Ad hoc items	x	*
Lifestyle (smoking, alcohol, physical activity, diet)	Ad hoc items	x	*
Family history of cancer	Ad hoc items	x	*
Part 2: Your everyday life			
Health-related Quality of Life	FACT-G/FACT-Lym	x	x
Part 3: How you are feeling			
Anxiety and depression	HADS	x	x
Intolerance to uncertainty	IUS Short form	x	
Part 4: Your support network			
Social support	Ad hoc items	x	x
Part 5: Medication and treatment			
Health literacy	Ad hoc items #	x	
Medication use and symptoms		x	x
Medication beliefs		x	x
Part 6: Opinions on cancer treatment and care			
Doctor-patient relationship	Ad hoc items ##	x	x
Treatment expectations		x	x

**only if changes occurred since baseline*

 # adapted for CAR T-cell therapy recipients

not included in the questionnaire for CAR T-cell therapy recipients

Abbreviations: FACT, Functional Assessment of Cancer Therapy (-G, general; -Lym, lymphoma); HADS, Hospital Anxiety and Depression Scale; IUS, Intolerance of Uncertainty Scale.

The first part of the questionnaire, issued at baseline, characterises the population based on sociodemographic and psychosocial factors. Subsequently, the questionnaire includes assessments of quality of life, anxiety, depression, (in)tolerance of uncertainty, social support, health literacy, medication-related beliefs and behaviours, relationship with their main physician and expectations of immunotherapy. The follow-up questionnaires will track longitudinal changes in these aspects. Patients will be invited to signal any change in their personal situation every time they take the

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questionnaire (e.g., patient stopped smoking, patient is now divorced, a new family member diagnosed with cancer) and will be asked to complete the rest of the questionnaire at each assessment. We will assess these features using ad hoc items and established questionnaires.

Ad hoc items explore various features in the QUALITOP questionnaire. First, they explore sociodemographic data (e.g., sex, age, number of children, marital status), gender roles (e.g., health responsibilities in a relationship), health habits (e.g., smoking, drinking, physical activity) and family history of cancer (e.g., number of family members who have or have had cancer, whether patients underwent genetic testing for cancer). Second, they explore the four main dimensions of social support [30] (material, informational, emotional, esteem) and how patients feel that they are available and provided by their partners (if applicable), family members and friends/loved ones. Third, they explore medication-related beliefs and behaviours, including physical discomfort, medication use, number of doctors usually consulted outside cancer care, self-medication, complementary care (e.g., physiotherapist, psychologist) and perception of so-called 'natural' medicines and practices. Finally, they explore opinions about cancer treatment and care, adapting items from the Treatment Representations Inventory [31] to immunotherapy for the doctor-patient relationship, perception of the level of information provided and expected side effects or outcomes.

The Functional Assessment of Cancer Therapy–General (FACT-G),[32] suitable for patients with any tumour type, will assess quality of life. This validated questionnaire has been widely used for this purpose since the nineties.[33,34] The FACT-Lym, which includes 15 additional tailored questions, will then be used for patients with lymphoma.[35] We will use the authorised Dutch, French, Portuguese and Spanish versions of each questionnaire.

The validated Dutch, French, Portuguese and Spanish versions of the Hospital Anxiety and Depression Scale (HADS) will be used to assess anxiety and depression longitudinally.[36–39] We aim to observe indicators of deterioration in quality of life and/or a response-shift phenomenon (i.e., adaptation and adjustment to the disease that allows quality of life to remain equivalent despite the

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illness).[40–43]

Immunotherapy remains an innovative treatment associated with uncertain treatment outcomes and side effects. Therefore, we will use the short version of the Intolerance of Uncertainty Scale (IUS Short Form) to assess possible difficulties with the management of uncertain situations.[44]

Health literacy, referring to the ability of individuals to access, understand, assess and use information and services for health, will be assessed using the Single-Item Literacy Screener (SILS). This has been validated in French and Spanish [45,46] and translated to Portuguese and Dutch. The SILS aims to measure participants' functional literacy; that is, their ability to understand information that might be necessary for their health.

Data collection in the historic cohort

For the historic databases, we aim to collect the same clinical data collected for patients in the prospective cohort. For patient-reported psychosocial data, inclusion will depend on its availability in each existing database. **Table 3** summarises the known data availability in the different historic databases, by domain, for the baseline and follow-up data.

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Table 3. Data availability for historic databases

	Immucare Elderly	Immucare Base	QoLD CART	OncoLifeS	Follow that CAR	eQuiPe	Xarxa Melanoma
Baseline data							
Lifestyle *(diet, alcohol, smoking)*	✓			✓			✓
Family history		✓		✓			✓
Sociodemographic factors	✓	✓		✓			
Physical well-being *(frailty, activities of daily living, performance status)*	✓	✓		✓	✓		
HRQoL			✓*	✓**	✓*/**	✓**	✓**
Medical history	✓	✓	✓	✓	✓		✓
Cancer characteristics *(diagnosis, staging, past treatments)*	✓	✓		✓	✓	✓	✓
Laboratory assessments	✓	✓		✓	✓		
Clinical assessments	✓	✓		✓	✓		✓
Follow-up data							
Lifestyle *(diet, alcohol, smoking)*							
Physical well-being *(frailty, activities of daily living, performance status)*		✓			✓		
HRQoL			✓	✓	✓		
Laboratory assessments		✓		✓	✓		
Clinical assessments		✓		✓	✓		✓
Adverse events	✓	✓	✓	✓	✓		✓
Survival	✓	✓	✓	✓	✓	✓	✓

**FACT-Lym (Functional Assessment of Cancer Therapy, lymphoma)*

*** EORTC-QLQ-C30*

Abbreviations: EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer core Quality of Life Questionnaire; FACT-Lym, Functional Assessment of Cancer Therapy, lymphoma; HRQoL, health-related quality of life.

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Data analysis plan

Data harmonisation and handling of missing data

To enable analyses with the data from the historical and/or prospective QUALITOP cohorts, we must first harmonise the generated data. Separate analyses may be required for the historical datasets given their heterogeneous structures. Although the structure of data to be collected for the prospective cohort has been harmonised beforehand, differences in patient populations, treatments and legislations between the five participating centres mean that differences will exist. Where these differences result in missing data, we will handle missingness separately for each analysis after careful consideration of the mechanism, paying close attention to associations between missingness, outcomes and exposures.[47] The method used will also depend on the nature of the statistical analysis, such as multiple imputation for regression-based methods [48] and the missing indicator approach for machine learning algorithms.[49] To capture heterogeneity between participating centres, we will include a centre effect in all the analyses as either fixed or random effects.[50]

Statistical analyses

We plan to use advanced statistical methods, machine learning techniques and mapping methods to exploit fully the vast amount of collected data and provide a deep understanding of the causal mechanisms underlying HRQoL, focusing on adverse events and individual characteristics.

The observational nature of the data will require specific methodologies. We will use tools developed in the framework of the potential outcomes,[51] such as inverse-probability-of treatment weighting,[52] doubly robust estimators[53] and targeted maximum likelihood estimation,[54] to account for confounding. Directed acyclic graphs,[55] informed by clinical frameworks like that depicted in **Figure 3**, will be developed in collaboration with partners to inform variable selection. These methods will help us to determine the causal effect of irAEs on HRQoL components. Intermediate analyses will be performed to identify the prognostic factors associated with irAEs, and

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boosting methods [56] will be used to determine those factors and their appropriate functional forms. The historical datasets will inform this step.

To further address the relationships between irAEs and HRQoL, we will use mediation analysis to disentangle the direct effect of individual characteristics and treatment on HRQoL, considering the effect mediated by irAEs.[57] This should uncover the factors driving HRQoL and could subsequently inform personalised care to maximise HRQoL. This stage will use machine learning algorithms, such as random forests,[58] to develop a prediction model for future HRQoL based on current demographic, psychosocial and clinical information.

The data collected in the QUALITOP project will benefit from repeated assessments of HRQoL over 18 months, facilitating the study of both individual trajectories over time and the causes and timing of changes in HRQoL. We will use mixed effect models and item response models to analyse the repeated measurements,[59] while simultaneously considering joint modelling to account for death as a competing event.[60]

We will then combine the outputs of the disparate analyses to develop a causal loop diagram to illustrate the complex web of medical and psychosocial factors affecting quality of life [61]. This diagram will inform the development and validation of a quantitative simulation model, using a system dynamics method to understand HRQoL after cancer immunotherapy under different hypothetical public health scenarios.

Medical data lake and smart digital platform

The QUALITOP project also aims to develop data management principles in a smart digital platform and associated medical data lake (**Figure 4**) that will enable networked medical agencies to share and exchange trusted and secure medical data with automated and robust controls based on FAIR (Findable, Accessible, Interoperable, Reusable) principles [62]. The digital platform will use the medical, psychological and psychosocial data collected in the historic and prospective QUALITOP

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cohorts. By employing monitoring technologies and advanced data analytics, the data lake and smart digital platform will allow for the determination of predictive markers in sub-populations associated with irAE development and HRQoL impairment. We will use data-driven automation, prediction, and decision support-analytics with technologies such as artificial intelligence (AI) to make predictions and recommendations for a given set of operator-defined objectives. By leveraging modern analytics and data management capabilities and working with AI methods such as machine learning to improve the HRQoL of patients undergoing immunotherapy and to minimise the risks of relapse, health care organisations can transform existing networks into smart digital health care ecosystems.

Patient monitoring using the smart digital platform

Finally, the smart digital platform aims to allow not only collaborative, integrated and personalised case monitoring but also actionable treatment adjustments or recommendations. These benefits will help reinforce treatment planning and improve the effectiveness of actions designed to reduce treatment effects, making room for the necessary corrective actions at different stages. Data from the historic Immucare database will be used to develop and test the clustering algorithms that will be integrated in the smart digital platform and used to simplify the data, look for patterns and similarities, and ultimately contribute to personalised patient monitoring.

ETHICS AND DISSEMINATION

Ethical considerations

The QUALITOP project will be conducted according to the Declaration of Helsinki. The local ethics committees of all participating centres have granted ethical approval. Patients will be invited to participate by their treating physician and will be required to provide signed informed consent. For the historic cohort, data from existing study databases and medical administrative registries will only

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be used if patients had provided signed informed consent that allowed the re-use of data for (international) scientific purposes. For analyses or dissemination activities at both national and international level, data will be protected under the European General Data Protection Regulation. The smart data platform and data lake will ensure privacy under the Security Rule of the Health Insurance Portability and Accountability Act. Moreover, the data lake will only include aggregated data, further ensuring anonymity.

Patient and public involvement

As 'experts by experience', patient representatives play a central role in reporting data on treatment outcomes, making their involvement key to the success of this project. Involvement will be facilitated by embedding the QUALITOP project in the European Cancer Patients Coalition as a health research project on big data and personalised medicine. This will provide invaluable opportunities to gain input and advice from patients and their relatives. In addition, the QUALITOP project can be followed on twitter, through a regular dedicated newsletter and through online events for patients with cancer. In the online meetings, researchers and partners of QUALITOP project can give a comprehensive overview of the project and how it can improve the quality of life of patients. At the same time, patients with cancer will have the opportunity to express their concerns, describe their experiences and give valuable feedback regarding the project. Thus, we offer various routes for proactive and reactive patient involvement to ensure that the research meets the needs and wishes of patients and their families. More detail about these routes to patient and public involvement can be found at the following links:

- European Cancer Patients Coalition: https://ecpc.org/health-and-research/qualitop/
- Twitter: @h2020qualitop
- QUALITOP news and event: https://h2020qualitop.liris.cnrs.fr/wordpress/index.php/
- QUALITOP LinkedIn: https://www.linkedin.com/company/qualitop-h2020/

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Dissemination

Continuing from the strong patient and public involvement throughout the earlier stages of the study, we will ensure that our results are not only presented at patient organisation meetings but also distributed through national and social media. Furthermore, professional engagement will be stimulated by presenting the study results at national and international conferences and by submitting manuscripts to peer-reviewed scientific journals. All results will be reported following current standards (e.g., STROBE guidelines).[63] The final product of the QUALITOP project, the smart digital platform, will also play a central role in the dissemination of information to various stakeholders, underpinned by a big medical data lake of aggregated data from the project's various data sources. This platform will use secured portals that are accessible to each major stakeholder group and will include functions and information tailored to their specific needs (**Table 4**).

Table 4. Specific outcomes expected by key stakeholder group

Stakeholder	Expected benefits
Patients	• Provide information and feedback on irAE risks, tips, recommendations and evidence-based results from up-to-date studies • Connections with peers (develop peer support) through a web-based platform • Provide education • Allow registration as participants to the QUALITOP cohort
Patients' relatives	• Provide information about their relative's disease, treatment and irAEs (evidence-based results from up-to-date studies) • Ease connections with other relatives (similar to the peer support for patients)
Haematologists, oncologists and other healthcare providers	• Provide information about irAEs, symptomatic treatments and patients' behaviour regarding self-treatment
The general population	• Provide information (metadata and syntheses of the most up-to-date information regarding HRQoL after cancer immunotherapy and its determinants) • Communicate policies and recommendations
Scientists and policymakers	• Provide data-driven analysis functions and sharing of health economic data, conclusions and policies
Abbreviations: HRQoL, health-related quality of life; irAE, immune-related adverse events.	

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DISCUSSION

The QUALITOP project aims to develop and implement a digital immunotherapy platform in Europe. It will use big data analysis, AI and simulation modelling approaches to collect and aggregate real-world HRQoL data, monitor patients' health statuses, conduct causal inference analyses, create harm-reduction recommendations for patients and other stakeholders, and disseminate findings efficiently and effectively. The planned data analyses should expand scientific knowledge about the complex interplay between clinical factors, psychosocial factors and long-term quality of life in a real-life setting after immunotherapy. Beyond this, we plan to use the acquired data and knowledge to nourish a smart digital platform that should offer a host of benefits to various stakeholders. Of course, we anticipate challenges on the path to achieving these outcomes. For example, the COVID-19 pandemic has already affected patient inclusion in the QUALITOP cohorts, which we were able to resolve be receiving a six-month extension from the European Union. Potential effects on treatment regimens and HRQoL may need to be considered in the statistical analyses. We also anticipate regulatory challenges for the smart digital platform, but by respecting the strict European regulations that exist to ensure patient privacy, we expect to deliver this with little difficulty. The QUALITOP project will expand knowledge about the health statuses and quality of life of patients after treatment with either ICI or CAR T-cells in real-world settings, delivering a smart digital platform that can empower cancer patients and inform health care providers. We hope that this project will illustrate that, by making use of smart digital solutions, international collaborations can accelerate the acquisition and dissemination of scientific knowledge surrounding cancer treatment.

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DECLARATIONS

Author Contributions

All authors have contributed to the conception and design of this study protocol. PCV, MC, GHdB, SP and DMB drafted the manuscript. All other authors have offered critical revision of the manuscript for important intellectual content. All authors have read and approved the final manuscript.

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Competing interests

MJK: honoraria from Kite, a Gilead Company, Novartis and Miltenyi Biotech, Roche, and Bristol Myers Squibb/Celgene; consultancy or advisory role for Kite, a Gilead Company, Roche, Novartis, Bristol Myers Squibb/Celgene, and Miltenyi Biotech; research funding from Kite, a Gilead Company, Roche, Takeda, and Celgene; and travel support from Kite, a Gilead Company, Roche, Novartis and Miltenyi Biotech. All other authors declare that they have no competing interests.

Availability of data and materials

Data will be made available upon reasonable request after an embargo period (i.e. after publishing our results) and subject to receiving relevant research questions. Due to the high sensitivity and privacy of the data we collect (protected by European law), we will only allow access to the data for a predefined time. Access will always be in accordance with informed consent and relevant national laws. For this study, the metadata about the study will be published in a public repository.

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FIGURE LEGENDS

Figure 1. Structure of the QUALITOP project.

Figure 2. Timeline of patient monitoring in the historic and prospective cohorts of the QUALITOP project.

Figure 3. Framework for the medical and psychosocial determinants of quality of life.

Figure 1. Simplified representation of the architecture of the Smart Data Platform and its underlying medical data lake.

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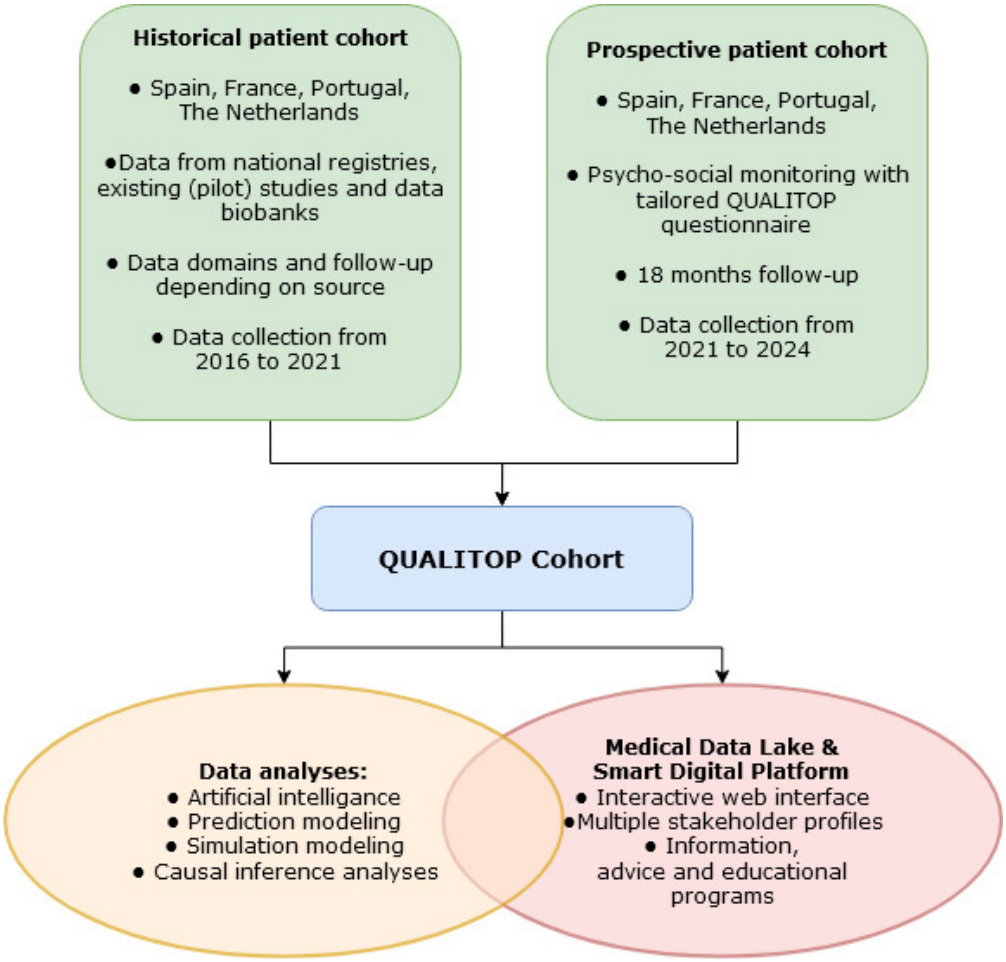

Structure of the QUALITOP project.

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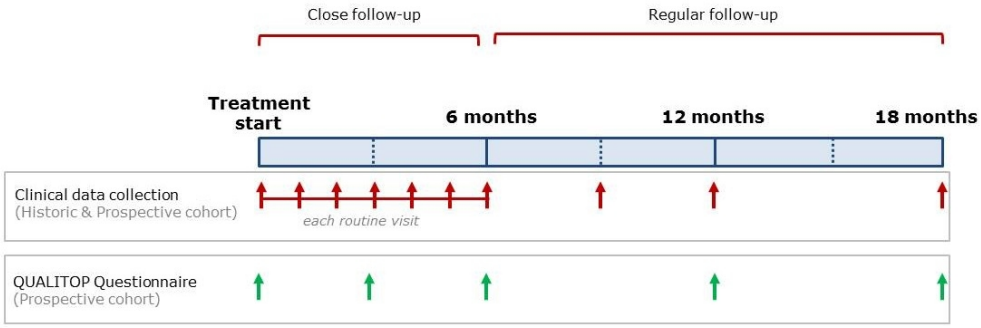

Timeline of patient monitoring in the historic and prospective cohorts of the QUALITOP project.

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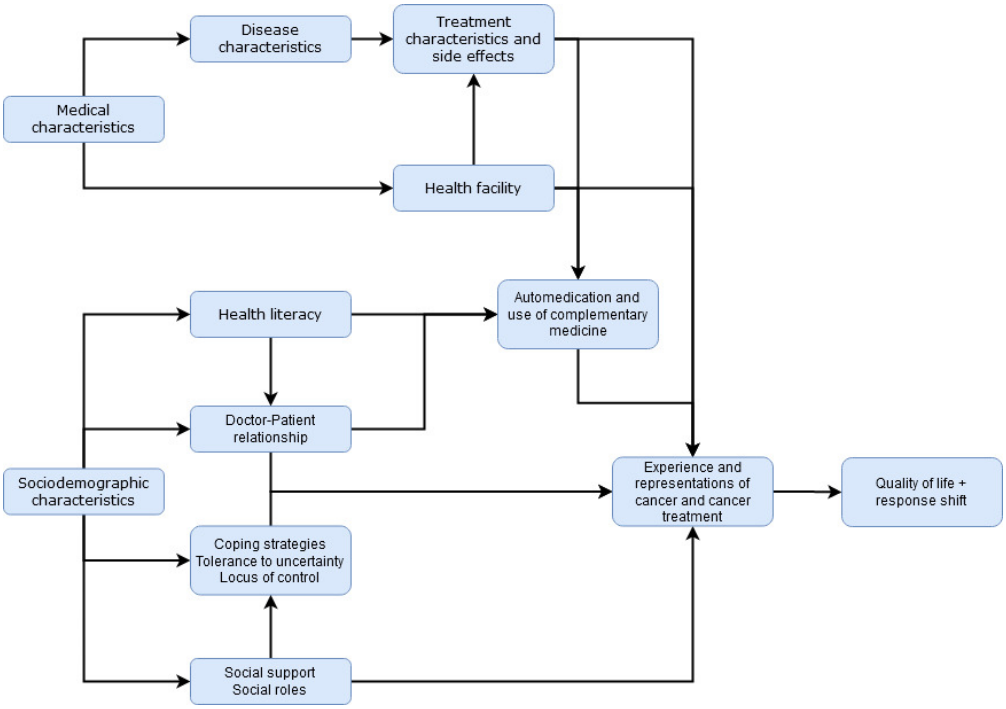

Framework for the medical and psychosocial determinants of quality of life.

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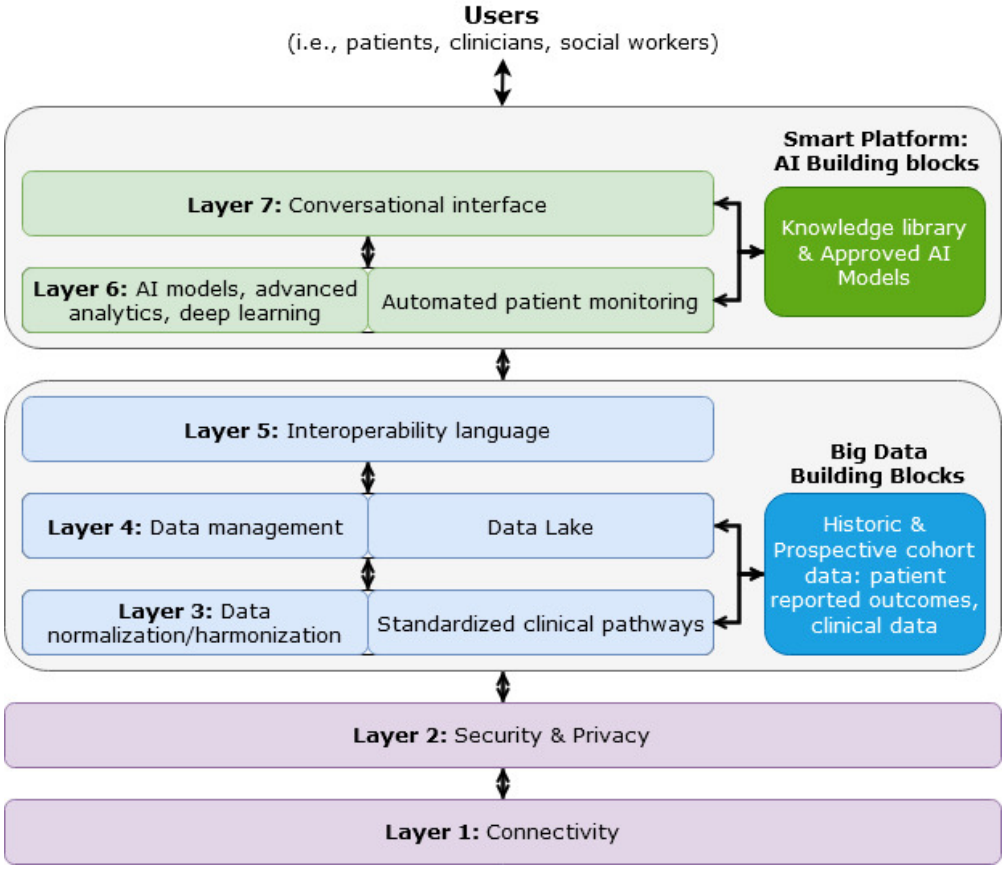

Simplified representation of the architecture of the Smart Data Platform and its underlying medical data lake.

219x189mm (72 x 72 DPI)

Supplement 1: Data sources from each participating nation

Data sources

Patient data for both the historic and prospective cohorts will come from various existing and new databases in France, the Netherlands, Portugal and Spain.

France

The QUALITOP cohort from France includes three historic and two prospective databases from Hospices Civils de Lyon (**Table 1**). The historic IMMUCARE ELDERLY cohort focused on clinical outcomes and irAEs after initiating ICI monotherapy or combination therapy between 2007 and 2019, with follow-up until late 2020. Data collected in the IMMUCARE BASE from 2019 in a clinical trial ('A Clinical and Biological Prospective Database of Patients Treated with Anticancer Immunotherapy and Follow-up of Their Immune-related Adverse Events irAE', registered NCT03989323 in clinicaltrial.gov) constitute the second historic cohort. This collected data for approximately 550 patients from the start of ICI treatment, irrespective of cancer type. Since August 2021, the study has included the QUALITOP quality of life questionnaires, demarcating the start of the prospective IMMUCARE BASE QUALITOP cohort. Earlier, in April 2021, the QoLD CART study began the prospective monitoring of HRQoL using the FACT-Lym for patients with diffuse large B-cell lymphoma receiving CAR T-cell therapy. Patients diagnosed with lymphoma who receive CAR T-cell therapy will be invited to a prospective QUALITOP cohort.

The Netherlands

We will include three historic and two prospective databases from the Netherlands. The OncoLifeS data biobank has collected data on clinical well-being and quality of life (assessed by EORTC-QLQ C30) since 2015 for patients with an oncological diagnosis treated in the University Medical Center Groningen.[29] Quality of life is monitored for 2 years after treatment and clinical outcomes are

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monitored continuously. We extracted additional data on irAEs for a historic cohort of approximately 500 patients with lung cancer who received ICIs and will use the same processes to collect the prospective data. Amsterdam University Medical Centers will lead the data collection for patients treated with CAR T-cell therapy in the Netherlands from January 2020, using data from the nationwide 'Follow that CAR' biobank initiated by the Dutch National CAR-T Tumor Board. This biobank has prospectively monitored clinical outcomes and quality of life, using the FACT-Lym, for patients with diffuse large B-cell lymphoma treated with CAR T-cell therapy. The historic cohort comprises approximately 40 patients, and the same process will be used to collect the prospective data. Lastly, the eQuiPe study collected data on quality of life for patients with advanced cancers in the Netherlands and is linked to the Netherlands Cancer Registry. The data from this study are included as a historic cohort.

Portugal

The Instituto Português de Oncologia in Lisboa invited patients diagnosed with lymphoma treated with CAR T-cell therapy or ICIs to participate in the prospective QUALITOP cohort from the end of 2021 onwards. No historical patient data are available.

Spain

The Hospital Clinic of Barcelona has asked patients treated for melanoma to consent to the inclusion of their data in the "Xarxa de Melanoma de Catalunya" database since 2016. This database allows participating centres to investigate phenotypic, genetic and disease evolution in patients, using biomaterials, including DNA, stored in the "Colecció de la Unitat de melanoma" (IDIBAPS registry code: R120904-090, National ISCIII registry code: C.0000334). Since January 2020, they have collected data on clinical well-being and quality of life (assessed by EORTC-QLQ C30) for patients with melanoma treated with ICIs. We have included approximately 50 patients in a historical melanoma cohort and will use the same process for the prospective data collection.

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓
Objectives	3	State specific objectives, including any prespecified hypotheses	✓
Methods			
Study design	4	Present key elements of study design early in the paper	✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓
Bias	9	Describe any efforts to address potential sources of bias	✓
Study size	10	Explain how the study size was arrived at	N.A.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N.A.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓
		(*b*) Describe any methods used to examine subgroups and interactions	N.A.
		(*c*) Explain how missing data were addressed	✓
		(*d*) If applicable, explain how loss to follow-up was addressed	N.A.
		(*e*) Describe any sensitivity analyses	N.A.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N.A.
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N.A.
		(b) Indicate number of participants with missing data for each variable of interest	N.A.
		(c) Summarise follow-up time (eg, average and total amount)	N.A.
Outcome data	15*	Report numbers of outcome events or summary measures over time	N.A.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	N.A.

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		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N.A.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N.A.
Discussion			
Key results	18	Summarise key results with reference to study objectives	N.A.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N.A.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N.A.
Generalisability	21	Discuss the generalisability (external validity) of the study results	N.A.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Monitoring multidimensional aspects of quality of life after cancer immunotherapy: protocol for the international multi-centre, observational QUALITOP cohort study

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Keywords:	Adverse events < THERAPEUTICS, ONCOLOGY, Epidemiology < ONCOLOGY

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Monitoring multidimensional aspects of quality of life after cancer immunotherapy: protocol for the international multi-centre, observational QUALITOP cohort study

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ABSTRACT

Introduction: Immunotherapies, such as immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy, have significantly improved the clinical outcomes of various malignancies. However, they also cause immune-related adverse events (irAEs) that can be challenging to predict, prevent and treat. Although they likely interact with health-related quality of life (HRQoL), most existing evidence on this topic has come from clinical trials with eligibility criteria that may not accurately reflect real-world settings. The QUALITOP project will study HRQoL in relation to irAEs and its determinants in a real-world study of patients treated with immunotherapy.

Methods and analysis: This international, observational, multi-centre study takes place in France, the Netherlands, Portugal and Spain. We aim to include about 1800 adult cancer patients treated with immunotherapy in a specifically recruited prospective cohort, and to additionally obtain data from historical real-world databases (i.e. databiobanks) and medical administrative registries (i.e. national cancer registries) in which relevant data regarding other adult cancer patients treated with immunotherapy has already been stored. In the prospective cohort, clinical health status, HRQoL and psychosocial well-being will be monitored until 18 months after treatment initiation through questionnaires (at baseline and 3, 6, 12 and 18 months thereafter), and by data extraction from electronic patient files. Using advanced statistical methods, including causal inference methods, artificial intelligence algorithms and simulation modelling, we will use data from the QUALITOP cohort to improve the understanding of the complex relationships between treatment regimens, patient characteristics, irAEs and HRQoL.

Ethics and dissemination: All aspects of the QUALITOP project will be conducted in accordance with the Declaration of Helsinki and with ethical approval from a suitable local ethics committee, and all patients will provide signed informed consent. In addition to standard dissemination efforts in the scientific literature, the data and outcomes will contribute to a smart digital platform and medical data lake. These will (1) help increase knowledge about the impact of immunotherapy, (2) facilitate

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improved interactions between patients, clinicians and the general population, and (3) contribute to personalised medicine.

Registration: This study is registered at ClinicalTrials.gov under identifier NCT05626764.

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Keywords

Neoplasms, Immunotherapy, Quality of Life, Drug-related Side Effects and Adverse Reactions, Immune Check Point Inhibitors, Receptors, Chimeric Antigen

Strengths and limitations of this study

- The QUALITOP project will create an international, multi-centre, real-world cohort that aggregates data of multiple types and from multiple sources.
- The collected data will contribute to a medical data lake underlying a smart digital platform, which may be used by various stakeholders.
- Despite its potential benefits, the QUALITOP project relies on data from heterogeneous patient groups and from partly validated patient questionnaires.
- As this project started during the COVID-19 pandemic, we expect to limit recruitment shortage by study extension and enrichment of historical databases with retrospective data.

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INTRODUCTION

Cancer immunotherapy has revolutionised oncology care over the last two decades, adding to the existing therapeutic arsenal through its unique action in stimulating the immune system to recognise and attack cancer cells.[1] Two subtypes of immune intervention that have gained particular interest, namely immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T cells (CAR T-cells), have hugely different mechanisms of action, indications and adverse events. Moreover, we lack long-term data on their health effects due to their relative novelty. International registries that monitor patient well-being in real-life settings provide invaluable opportunities to fill such knowledge gaps.

Immunotherapies trigger unique toxicities by activating the immune system to attack healthy cells. These immune-related adverse events (irAEs) occur in up to 96% of patients who receive ICIs, with severe irAEs reported in 10%–28% of patients receiving ICI monotherapy (Common Terminology Criteria for Adverse Events, grade ≥3) [2–5] and 59% of patients receiving combination therapy.[5] Dermatological, gastrointestinal and endocrine irAEs are most common, and management varies from symptomatic treatment for mild (grade 1–2) irAEs to corticosteroid or immunosuppressant (e.g., infliximab) treatment, or even permanent immunotherapy cessation, for life-threatening (grade 4) irAEs.[6] Nevertheless, toxicity profiles after ICI therapy appear more favourable than those of chemotherapy, with lower risks of developing any AEs or severe AEs (grade ≥3) for immunotherapy.[7] CAR T-cell therapy also causes various treatment-specific irAEs, with cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, infection and cytopenia the most common and severe in the acute phase (<28 days after CAR T-cell infusion).[8] Although irAEs can be life-threatening, they are usually reversible with early intervention. The most common long-term side effects are ongoing cytopenias, impaired immune reconstitution with B-cell aplasia, T-cell depletion and hypogammaglobulinemia with increased risk of infection.[9]

Besides improved clinical outcomes, immunotherapy should offer the patient psychosocial benefits

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compared with conventional therapies. To this end, trials have reported smaller impairments in health-related quality of life (HRQoL), longer times to HRQoL deterioration and better control of cancer symptoms.[10,11] However, immunotherapies and their associated irAEs may still affect HRQoL given that we know little of their associated late-onset and long-lasting effects.[12] Moreover, although Immunotherapy has clear and proven benefits over conventional anticancer treatments,[10,11,13–19] this evidence has predominantly come from clinical trials that have strict eligibility criteria. These data may exclude patients with poor performance status (Eastern Cooperative Oncology Group, performance status >1), concomitant cancers, auto-immune diseases or long-term systemic corticosteroid use.[3,20] Therefore, we do not know if the clinical and psychosocial benefits of immunotherapy in trial settings apply to real-world cohorts. The growth in survivor populations as these treatments elicit durable clinical responses and long-term remission for malignancies that previously had poor prognoses [21] emphasises the need for research into the long-term well-being and HRQoL of patients treated with these therapies.

We aim to study the multidimensional aspects of patients' HRQoL, the irAEs that develop during ICI and CAR T-cell therapy, and the relevant determinants of both, using a purpose-built smart digital platform with a medical data lake. This digital platform will improve data provision to various stake holders about risk profiles for irAE development or HRQoL deterioration. In this way, we can improve personalised and shared decision making for future patients eligible for immunotherapy.

METHODS AND ANALYSIS

Study design

The *'Monitoring multidimensional aspects of **Qua**lity of **Li**fe after cancer **I**mmuno**T**herapy, an **O**pen smart digital **P**latform for personalised prevention and patient management'* (QUALITOP) project is an international, multi-centre, real-world, observational cohort study. We will provide insights into

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the medical and psychosocial determinants of quality of life after cancer immunotherapy, making use of big data analyses, artificial intelligence and simulation modelling, before integrating the results in an information technology platform developed for the project. Additional information can be found on the project's website.[22] This study is registered at ClinicalTrials.gov under identifier NCT05626764.

We will study adverse events and quality of life among patients with cancer during and after immunotherapy. The QUALITOP cohort will combine a historical cohort of existing patients and a prospective cohort enrolled specifically for this project (**Figure 1**). The historical cohort will comprise patient data routinely collected in existing databases and medical registries in Spain, France, Portugal and the Netherlands, for which existing informed consent allows the re-use of data within the context of this European collaboration. For the prospective cohort, patients will be recruited in the same countries under the coordination of Hospital Clinic de Barcelona (IDIBAPS), Hospices Civils de Lyon, Instituto Português de Oncologia Lisboa, and Amsterdam University Medical Centers and University Medical Center Groningen, respectively. **Figure 2** shows the study timeline. Note that patients will not be included in both the historic and prospective cohorts.

Patient selection

Patients will be eligible for inclusion in a cohort if they are aged ≥18 years at the time of signing informed consent and have an oncological diagnosis either treated or to be treated with ICIs or CAR T-cells (as monotherapy or in combination with other anticancer treatments). Patients treated as part of a clinical trial may also be included if permitted by the clinical trial. However, we will exclude patients who are pregnant, under guardianship or who refuse to sign informed consent. For the prospective cohort, patients can be recruited from the decision for immunotherapy until their second cycle of immunotherapy. Patients receiving CAR T-cell therapy will be recruited from after leukapheresis to the start of lymphodepleting chemotherapy, before CAR T-cell infusion. For the prospective cohort, patients will be asked to participate by trained members of the medical staff,

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such as doctors and (research) nurses, during visits that are part of regular care. Based on the average number of eligible patients treated in the participating clinical centres, we aim to include about 1800 patients in the prospective cohort.

Study outcomes

The primary outcome of the QUALITOP study is HRQoL, combining the patient's perspective of their physical, psychological and social functioning.[23] We will measure this outcome repeatedly in the prospective cohort and obtain data for a selection of patients and time points in the historic cohort. The secondary outcome of the QUALITOP study is the incidence and severity of irAEs, which we will extract from the electronic records for patients in both cohorts.

Data collection

Overview of data sources and timeline

Patient data for both the historic and prospective cohorts will come from existing and new databases at sites in France, the Netherlands, Portugal and Spain, as summarised in Table 1 and detailed in Supplemental File 1. Each study site has different specialisations and will cover different oncological diagnoses and therapies.

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Table 1. Overview of data sources and their population characteristics per country

Study site	Name of existing study/database	Cohort + period of data collection	Oncological diagnosis	Therapy
France				
Hospices Civils de Lyon	Immucare Elderly	Historical (2007–2020)	Any solid tumour	ICIs
Hospices Civils de Lyon	Immucare BASE	Historical (2019 onward) Prospective (2021 onward)	Any solid tumour	ICIs
Hospices Civils de Lyon	QoLD CART	Historical (2021 onward)	Lymphoma	CAR T-cells
Hospices Civils de Lyon	QUALITOP CART	Prospective (2022 onward)	Lymphoma	CAR T-cells
The Netherlands				
University Medical Center Groningen	OncoLifeS	Historical (2015 onward) Prospective (2021 onward)	Lung cancer	ICIs
Nationwide CAR-T cohort	Follow that CAR	Historical (2020–2021) Prospective (2021 onward)	Lymphoma	CAR T-cells
Nationwide Cancer Registry (IKNL)	eQuiPe	Historical (2016–2020)	Any malignancy	Any treatment
Portugal				
Instituto Português de Oncologia, Lisboa	QUALITOP Lymphoma	Prospective (2021 onward)	Lymphoma	CAR T-cells, ICIs
Spain				
Hospital Clinic de Barcelona (IDIBAPS)	Xarxa Melanoma	Historical (2020–2021) Prospective (2021 onward)	Melanoma	ICIs
Abbreviations: CAR, chimeric antigen receptor; ICIs, immune checkpoint inhibitors.				

Figure 2 shows the proposed timeline of patient monitoring in the historic and prospective cohorts. Data for eligible patients from the historic cohorts were collected between 2016 and 2021, while patient inclusion for the prospective cohorts was initiated in April 2021 and will continue until January 2023. Afterwards, inclusion is intended to be continued in a sustainability programme. We will monitor patients closely for the first 6 months of treatment or until cessation, after which patients will enter a phase of less intensive monitoring until 18 months after treatment initiation or the QUALITOP project ends (**Figure 2**). Clinical data will be manually extracted from electronic patient files for both cohorts. The QUALITOP questionnaire, which aims to collect data from various psychosocial domains, will only be used in the prospective cohort.

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Data collection in the prospective cohort

Except in France, data from the prospective arm of the cohort are being collected and managed in REDCap (Research Electronic Data Capture), hosted by the participating institutions.[24,25] REDCap is a secure, web-based platform designed to support data capture for research studies. It provides the following: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. In France, data collection is being managed in Easily, a web-based electronic health record platform developed locally and hosted at Hospices Civils de Lyon. The database structure fits the common set of covariates in QUALITOP.

Clinical data

Clinical data will be manually extracted from electronic patient files for each routine visit in the first 6 months of treatment and at fixed timepoints in the following year (9, 12 and 18 months). The timing of routine visits will differ by treatment type (ICI or CAR T-cell). We will assess medical history, medication use, prior anticancer treatments and cancer characteristics at the initiation of immunotherapy. Both at baseline and during follow-up, we will collect data from physical examinations (i.e., weight, performance status, blood pressure), laboratory assessments (i.e., C-reactive protein, neutrophils, leukocytes) and related to irAEs according to the Common Terminology Criteria for Adverse Events, version 5, of the National Cancer Institute.[26] Data about treatment for irAEs will be collected according to BioPortal's Drug Ontology,[27] available in REDCap. We will evaluate treatment response using the RECIST criteria for solid tumours [28] and the Lugano criteria for lymphomas.[29] Examples of data collected within the domains specified above can be found in Supplement 2.

Psychosocial questionnaires

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We developed psychosocial questionnaires to assess the multiple dimensions of quality of life and its potential psychosocial determinants in patients, necessary for the minimal data set of each patient included in the prospective cohort. A more in-depth questionnaire is issued at baseline and a shorter version is issued during follow-up at 3, 6, 12 and 18 months. We also modified the questionnaire slightly for patients receiving CAR T-cell therapy. **Table 2** summarises the domains included in each version of the questionnaire. The questionnaire as a whole was not pre-tested (because it was constructed during the COVID-19 pandemic, and it was not possible to meet with patients). However, it was reviewed by oncologists in all the countries involved in the data collection.

The flowchart in **Figure 3** illustrates the hypothesised framework for the interrelatedness of the questionnaire domains and their association with quality of life. We created French, English, Portuguese, Spanish and Dutch versions of the questionnaires, and when no validated translation existed, an external service provider specialising in academic and medical translation completed the translation. A researcher in each country also proofread the questionnaires, ensuring that the English version was consistent with his/her language.

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Table 2. QUALITOP questionnaire domains at baseline and during follow-up

Questionnaire domains	Source	Baseline	Follow-up (3, 6, 12, 18 months)
Part 1: Personal and work situation			
Sociodemographic factors (work, education, family and living situation)	Ad hoc items	x	*
Gender roles	Ad hoc items	x	*
Lifestyle (smoking, alcohol, physical activity, diet)	Ad hoc items	x	*
Family history of cancer	Ad hoc items	x	*
Part 2: Your everyday life			
Health-related Quality of Life	FACT-G/FACT-Lym	x	x
Part 3: How you are feeling			
Anxiety and depression	HADS	x	x
Intolerance to uncertainty	IUS Short form	x	
Part 4: Your support network			
Social support	Ad hoc items	x	x
Part 5: Medication and treatment			
Health literacy	Ad hoc items #	x	
Medication use and symptoms		x	x
Medication beliefs		x	x
Part 6: Opinions on cancer treatment and care			
Doctor-patient relationship	Ad hoc items ##	x	x
Treatment expectations		x	x

**only if changes occurred since baseline*

 # adapted for CAR T-cell therapy recipients

not included in the questionnaire for CAR T-cell therapy recipients

Abbreviations: FACT, Functional Assessment of Cancer Therapy (-G, general; -Lym, lymphoma); HADS, Hospital Anxiety and Depression Scale; IUS, Intolerance of Uncertainty Scale.

The first part of the questionnaire, issued at baseline, characterises the population based on sociodemographic and psychosocial factors. Subsequently, the questionnaire includes assessments of quality of life, anxiety, depression, (in)tolerance of uncertainty, social support, health literacy, medication-related beliefs and behaviours, relationship with their main physician and expectations of immunotherapy. The follow-up questionnaires will track longitudinal changes in these aspects. Patients will be invited to signal any change in their personal situation every time they take the

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questionnaire (e.g., patient stopped smoking, patient is now divorced, a new family member diagnosed with cancer) and will be asked to complete the rest of the questionnaire at each assessment. We will assess these features using ad hoc items and established questionnaires.

Ad hoc items explore various features in the QUALITOP questionnaire. Ad-hoc items are used for domains for which no suitable validated questions/questionnaires were available. The items are based on expert opinions and prior experience with research in similar patient populations. Especially for domains 5 ("Medication and treatment") and 6 ("Opinions on cancer treatment and care"), clinicians' knowledge and experience with immunotherapy treatment was of key importance in developing and evaluating the ad hoc items.

First, ad hoc items explore sociodemographic data (e.g., sex, age, number of children, marital status), gender roles (e.g., health responsibilities in a relationship), health habits (e.g., smoking, drinking, physical activity) and family history of cancer (e.g., number of family members who have or have had cancer, whether patients underwent genetic testing for cancer). Second, they explore the four main dimensions of social support [30] (material, informational, emotional, esteem) and how patients feel that they are available and provided by their partners (if applicable), family members and friends/loved ones. Third, they explore medication-related beliefs and behaviours, including physical discomfort, medication use, number of doctors usually consulted outside cancer care, self-medication, complementary care (e.g., physiotherapist, psychologist) and perception of so-called 'natural' medicines and practices. Finally, they explore opinions about cancer treatment and care, adapting items from the Treatment Representations Inventory [31] to immunotherapy for the doctor-patient relationship, perception of the level of information provided and expected side effects or outcomes.

The Functional Assessment of Cancer Therapy–General (FACT-G),[32] suitable for patients with any tumour type, will assess quality of life. This validated questionnaire has been widely used for this purpose since the nineties.[33,34] The FACT-Lym, which includes 15 additional tailored questions,

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will then be used for patients with lymphoma.[35] We will use the authorised Dutch, French, Portuguese and Spanish versions of each questionnaire.

The validated Dutch, French, Portuguese and Spanish versions of the Hospital Anxiety and Depression Scale (HADS) will be used to assess anxiety and depression longitudinally.[36–39] We aim to observe indicators of deterioration in quality of life and/or a response-shift phenomenon (i.e., adaptation and adjustment to the disease that allows quality of life to remain equivalent despite the illness).[40–43]

Immunotherapy remains an innovative treatment associated with uncertain treatment outcomes and side effects. Therefore, we will use the short version of the Intolerance of Uncertainty Scale (IUS Short Form) to assess possible difficulties with the management of uncertain situations.[44]

Health literacy, referring to the ability of individuals to access, understand, assess and use information and services for health, will be assessed using the Single-Item Literacy Screener (SILS). This has been validated in French and Spanish [45,46] and translated to Portuguese and Dutch. The SILS aims to measure participants' functional literacy; that is, their ability to understand information that might be necessary for their health.

Data collection in the historic cohort

For the historic databases, we aim to collect the same clinical data collected for patients in the prospective cohort. For patient-reported psychosocial data, inclusion will depend on its availability in each existing database. **Table 3** summarises the known data availability in the different historic databases, by domain, for the baseline and follow-up data.

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Table 3. Data availability for historic databases

	Immucare Elderly	Immucare Base	QoLD CART	OncoLifeS	Follow that CAR	eQuiPe	Xarxa Melanoma
Baseline data							
Lifestyle *(diet, alcohol, smoking)*	✓			✓			✓
Family history		✓		✓			✓
Sociodemographic factors	✓	✓		✓			
Physical well-being *(frailty, activities of daily living, performance status)*	✓	✓		✓	✓		
HRQoL			✓*	✓**	✓*/**	✓**	✓**
Medical history	✓	✓	✓	✓	✓		✓
Cancer characteristics *(diagnosis, staging, past treatments)*	✓	✓		✓	✓	✓	✓
Laboratory assessments	✓	✓		✓	✓		
Clinical assessments	✓	✓		✓	✓		✓
Follow-up data							
Lifestyle *(diet, alcohol, smoking)*							
Physical well-being *(frailty, activities of daily living, performance status)*		✓			✓		
HRQoL			✓	✓	✓		
Laboratory assessments		✓		✓	✓		
Clinical assessments		✓		✓	✓		✓
Adverse events	✓	✓	✓	✓	✓		✓
Survival	✓	✓	✓	✓	✓	✓	✓

**FACT-Lym (Functional Assessment of Cancer Therapy, lymphoma)*

*** EORTC-QLQ-C30*

Abbreviations: EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer core Quality of Life Questionnaire; FACT-Lym, Functional Assessment of Cancer Therapy, lymphoma; HRQoL, health-related quality of life.

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Data analysis plan

Data harmonisation and handling of missing data

To enable analyses with the data from the historical and/or prospective QUALITOP cohorts, we must first harmonise the generated data. Separate analyses may be required for the historical datasets given their heterogeneous structures. Although the structure of data to be collected for the prospective cohort has been harmonised beforehand, differences in patient populations, treatments and legislations between the five participating centres mean that differences will exist. Where these differences result in missing data, we will handle missingness separately for each analysis after careful consideration of the mechanism, paying close attention to associations between missingness, outcomes and exposures.[47] The method used will also depend on the nature of the statistical analysis, such as multiple imputation for regression-based methods [48] and the missing indicator approach for machine learning algorithms.[49] To capture heterogeneity between participating centres, we will include a centre effect in all the analyses as either fixed or random effects.[50]

Statistical analyses

We plan to use a broad variety of statistical methods for the purposes of description (e.g. describe baseline characteristics), explanation (e.g. explain changes in HRQoL by irAEs) and prediction (e.g. predict patients at risk for HRQoL deterioration through patient characteristics). In addition, we will use machine learning techniques and mapping methods to exploit fully the vast amount of collected data and provide a deep understanding of the causal mechanisms underlying HRQoL of patients treated with immunotherapy. A special focus lies on understanding the influence of adverse events and individual characteristics.

The observational nature of the data will require specific methodologies. We will use tools developed in the framework of the potential outcomes,[51] such as inverse-probability-of treatment weighting,[52] doubly robust estimators[53] and targeted maximum likelihood estimation,[54] to

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account for confounding. Directed acyclic graphs,[55] informed by clinical frameworks like that depicted in **Figure 3**, will be developed in collaboration with partners to inform variable selection. These methods will help us to determine the causal effect of irAEs on HRQoL components. Intermediate analyses will be performed to identify the prognostic factors associated with irAEs, and boosting methods [56] will be used to determine those factors and their appropriate functional forms. The historical datasets will inform this step.

To further address the relationships between irAEs and HRQoL, we will use mediation analysis to disentangle the direct effect of individual characteristics and treatment on HRQoL, considering the effect mediated by irAEs.[57] This should uncover the factors driving HRQoL and could subsequently inform personalised care to maximise HRQoL. This stage will use machine learning algorithms, such as random forests,[58] to develop a prediction model for future HRQoL based on current demographic, psychosocial and clinical information.

The data collected in the QUALITOP project will benefit from repeated assessments of HRQoL over 18 months, facilitating the study of both individual trajectories over time and the causes and timing of changes in HRQoL. We will use mixed effect models and item response models to analyse the repeated measurements,[59] while simultaneously considering joint modelling to account for death as a competing event.[60]

We will then combine the outputs of the disparate analyses to develop a causal loop diagram to illustrate the complex web of medical and psychosocial factors affecting quality of life [61]. This diagram will inform the development and validation of a quantitative simulation model, using a system dynamics method to understand HRQoL after cancer immunotherapy under different hypothetical public health scenarios.

Medical data lake and smart digital platform

The QUALITOP project also aims to develop data management principles in a smart digital platform

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and associated medical data lake (**Figure 4**) that will enable networked medical agencies to share and exchange trusted and secure medical data with automated and robust controls based on FAIR (Findable, Accessible, Interoperable, Reusable) principles [62]. The digital platform will use the medical, psychological and psychosocial data collected in the historic and prospective QUALITOP cohorts. By employing monitoring technologies and advanced data analytics, the data lake and smart digital platform will allow for the determination of predictive markers in sub-populations associated with irAE development and HRQoL impairment. We will use data-driven automation, prediction, and decision support-analytics with technologies such as artificial intelligence (AI) to make predictions and recommendations for a given set of operator-defined objectives. By leveraging modern analytics and data management capabilities and working with AI methods such as machine learning to improve the HRQoL of patients undergoing immunotherapy and to minimise the risks of relapse, health care organisations can transform existing networks into smart digital health care ecosystems.

Patient monitoring using the smart digital platform

Finally, the smart digital platform aims to allow not only collaborative, integrated and personalised case monitoring but also actionable treatment adjustments or recommendations. These benefits will help reinforce treatment planning and improve the effectiveness of actions designed to reduce treatment effects, making room for the necessary corrective actions at different stages. Data from the historic Immucare database will be used to develop and test the clustering algorithms that will be integrated in the smart digital platform and used to simplify the data, look for patterns and similarities, and ultimately contribute to personalised patient monitoring.

Patient and public involvement

As ‘experts by experience’, patient representatives play a central role in reporting data on treatment outcomes, making their involvement key to the success of this project. Involvement will be

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facilitated by embedding the QUALITOP project in the European Cancer Patients Coalition as a health research project on big data and personalised medicine. This will provide invaluable opportunities to gain input and advice from patients and their relatives. In addition, the QUALITOP project can be followed on twitter, through a regular dedicated newsletter and through online events for patients with cancer. In the online meetings, researchers and partners of QUALITOP project can give a comprehensive overview of the project and how it can improve the quality of life of patients. At the same time, patients with cancer will have the opportunity to express their concerns, describe their experiences and give valuable feedback regarding the project. Thus, we offer various routes for proactive and reactive patient involvement to ensure that the research meets the needs and wishes of patients and their families. More detail about these routes to patient and public involvement can be found at the following links:

- European Cancer Patients Coalition: https://ecpc.org/health-and-research/qualitop/
- Twitter: @h2020qualitop
- QUALITOP news and event: https://h2020qualitop.liris.cnrs.fr/wordpress/index.php/
- QUALITOP LinkedIn: https://www.linkedin.com/company/qualitop-h2020/

ETHICS AND DISSEMINATION

Ethical considerations

The QUALITOP project will be conducted according to the Declaration of Helsinki. The local ethics committees of all participating centres have granted ethical approval (Personal protection committee Hospices Civils de Lyon, Medical Ethics Committee University Medical Center Groningen, Medical Ethics Committee Amsterdam University Medical Centers, Ethics Committee for Health Instituto Português de Oncologia Lisboa, Ethics Committee Hospital Clinic of Barcelona) . Patients will be invited to participate by their treating physician and will be required to provide signed

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informed consent. For the historic cohort, data from existing study databases and medical administrative registries will only be used if patients had provided signed informed consent that allowed the re-use of data for (international) scientific purposes. For analyses or dissemination activities at both national and international level, data will be protected under the European General Data Protection Regulation. The smart data platform and data lake will ensure privacy under the Security Rule of the Health Insurance Portability and Accountability Act. Moreover, the data lake will only include aggregated data, further ensuring anonymity.

Dissemination

Continuing from the strong patient and public involvement throughout the earlier stages of the study, we will ensure that our results are not only presented at patient organisation meetings but also distributed through national and social media. Furthermore, professional engagement will be stimulated by presenting the study results at national and international conferences and by submitting manuscripts to peer-reviewed scientific journals. All results will be reported following current standards (e.g., STROBE guidelines).[63] The final product of the QUALITOP project, the smart digital platform, will also play a central role in the dissemination of information to various stakeholders, underpinned by a big medical data lake of aggregated data from the project's various data sources. This platform will use secured portals that are accessible to each major stakeholder group and will include functions and information tailored to their specific needs (**Table 4**).

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Table 4. Specific outcomes expected by key stakeholder group

Stakeholder	Expected benefits
Patients	• Provide information and feedback on irAE risks, tips, recommendations and evidence-based results from up-to-date studies • Connections with peers (develop peer support) through a web-based platform • Provide education • Allow registration as participants to the QUALITOP cohort
Patients' relatives	• Provide information about their relative's disease, treatment and irAEs (evidence-based results from up-to-date studies) • Ease connections with other relatives (similar to the peer support for patients)
Haematologists, oncologists and other healthcare providers	• Provide information about irAEs, symptomatic treatments and patients' behaviour regarding self-treatment
The general population	• Provide information (metadata and syntheses of the most up-to-date information regarding HRQoL after cancer immunotherapy and its determinants) • Communicate policies and recommendations
Scientists and policymakers	• Provide data-driven analysis functions and sharing of health economic data, conclusions and policies
Abbreviations: HRQoL, health-related quality of life; irAE, immune-related adverse events.	

DISCUSSION

The QUALITOP project aims to develop and implement a digital immunotherapy platform in Europe. It will use big data analysis, AI and simulation modelling approaches to collect and aggregate real-world HRQoL data, monitor patients' health statuses, conduct causal inference analyses, create harm-reduction recommendations for patients and other stakeholders, and disseminate findings efficiently and effectively. The planned data analyses should expand scientific knowledge about the complex interplay between clinical factors, psychosocial factors and long-term quality of life in a real-life setting after immunotherapy. Beyond this, we plan to use the acquired data and knowledge to nourish a smart digital platform that should offer a host of benefits to various stakeholders. Of course, we anticipate challenges on the path to achieving these outcomes. For example, the COVID-19 pandemic has already affected patient inclusion in the QUALITOP cohorts. We hope to resolve this with thereceived six-month extension from the European Union, as well as efforts to

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retrospectively enrich the historical databases that are part of QUALITOP. Potential effects on treatment regimens and HRQoL may need to be considered in the statistical analyses. We also anticipate regulatory challenges for the smart digital platform, but by respecting the strict European regulations that exist to ensure patient privacy, we expect to deliver this with little difficulty. The QUALITOP project will expand knowledge about the health statuses and quality of life of patients after treatment with either ICI or CAR T-cells in real-world settings, delivering a smart digital platform that can empower cancer patients and inform health care providers. We hope that this project will illustrate that, by making use of smart digital solutions, international collaborations can accelerate the acquisition and dissemination of scientific knowledge surrounding cancer treatment.

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DECLARATIONS

Author Contributions

PCV, MC, GHdB, CL, AMS, SD, MGdS, AFE, AR, MP, MSJ, AE, MP, MSH, CR, MJK, MGHvO, ESZ, AM, EC, AA, MP, MF, EC, SP and DMB have contributed to the conception and design of this study protocol. PCV, MC, GHdB, SP and DMB drafted the manuscript. PCV, MC, GHdB, CL, AMS, SD, MGdS, AFE, AR, MP, MSJ, AE, MP, MSH, CR, MJK, MGHvO, ESZ, AM, EC, AA, MP, MF, EC, SP and DMB have offered critical revision of the manuscript for important intellectual content. PCV, MC, GHdB, CL, AMS, SD, MGdS, AFE, AR, MP, MSJ, AE, MP, MSH, CR, MJK, MGHvO, ESZ, AM, EC, AA, MP, MF, EC, SP and DMB have read and approved the final manuscript.

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Competing interests

MJK: honoraria from Kite, a Gilead Company, Novartis and Miltenyi Biotech, Roche, and Bristol Myers Squibb/Celgene; consultancy or advisory role for Kite, a Gilead Company, Roche, Novartis, Bristol Myers Squibb/Celgene, and Miltenyi Biotech; research funding from Kite, a Gilead Company, Roche, Takeda, and Celgene; and travel support from Kite, a Gilead Company, Roche, Novartis and Miltenyi Biotech. All other authors declare that they have no competing interests.

Availability of data and materials

Data will be made available upon reasonable request after an embargo period (i.e. after publishing our results) and subject to receiving relevant research questions. Due to the high sensitivity and privacy of the data we collect (protected by European law), we will only allow access to the data for a predefined time. Access will always be in accordance with informed consent and relevant national

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laws. For this study, the metadata about the study will be published in a public repository.

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FIGURE LEGENDS

Figure 1. Structure of the QUALITOP project.

Figure 2. Timeline of patient monitoring in the historic and prospective cohorts of the QUALITOP project.

Figure 3. Framework for the medical and psychosocial determinants of quality of life.

Figure 1. Simplified representation of the architecture of the Smart Data Platform and its underlying medical data lake.

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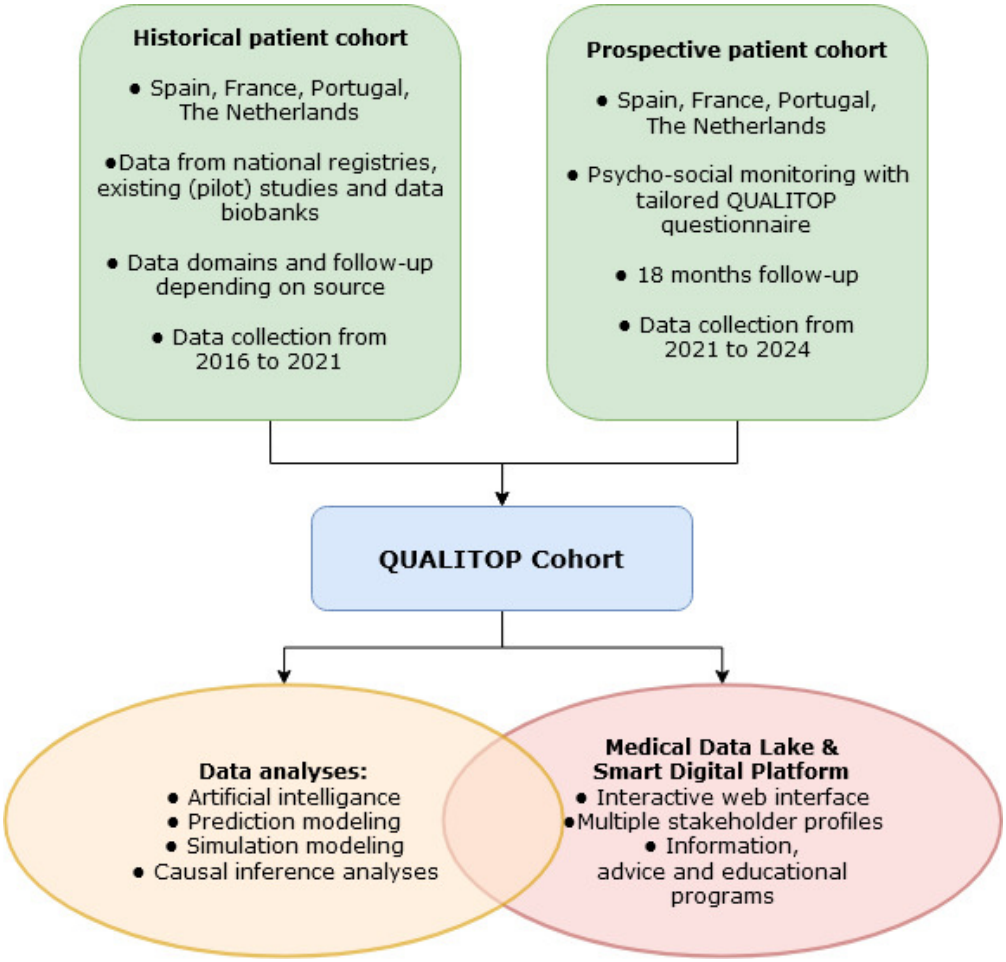

Structure of the QUALITOP project.

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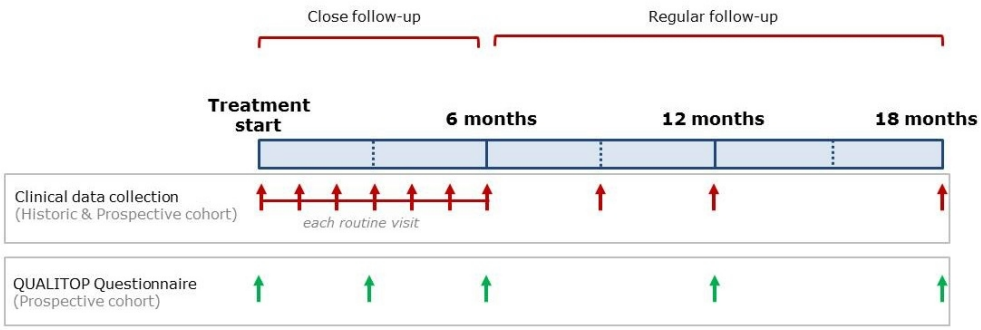

Timeline of patient monitoring in the historic and prospective cohorts of the QUALITOP project.

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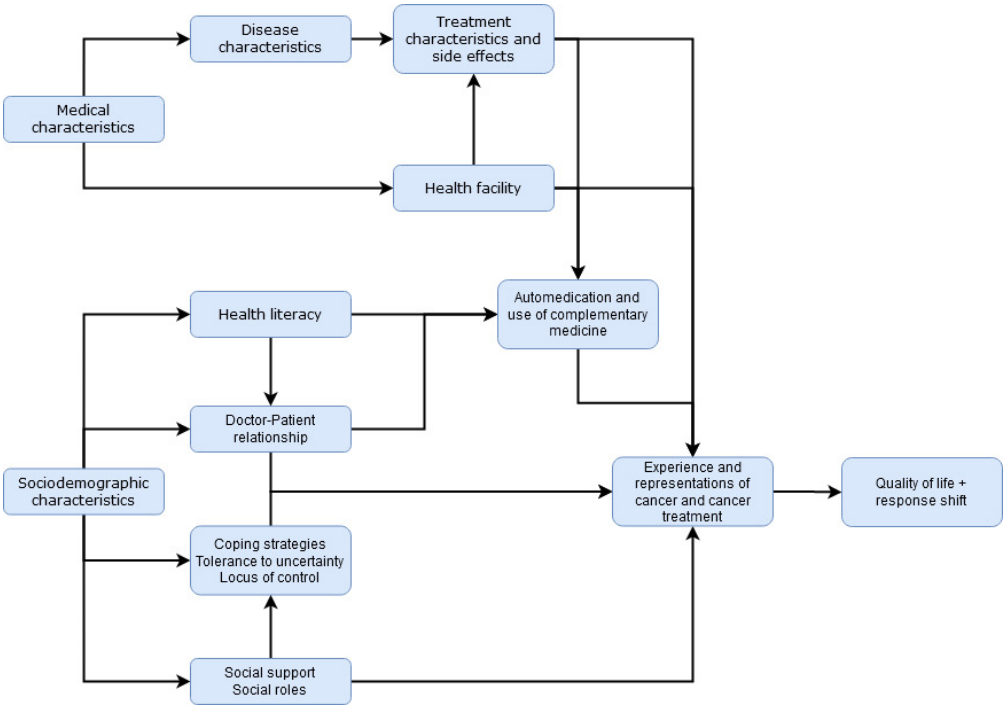

Framework for the medical and psychosocial determinants of quality of life.

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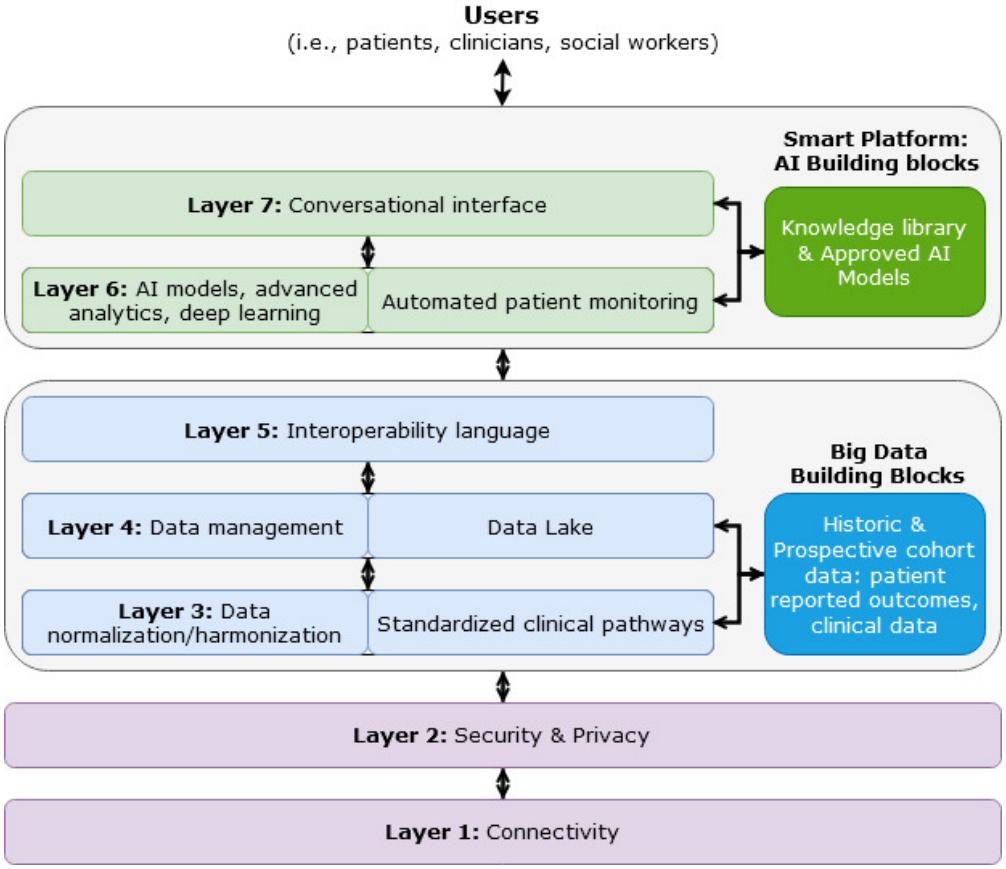

Simplified representation of the architecture of the Smart Data Platform and its underlying medical data lake.

219x189mm (72 x 72 DPI)

Supplement 1: Data sources from each participating nation

Data sources

Patient data for both the historic and prospective cohorts will come from various existing and new databases in France, the Netherlands, Portugal and Spain.

France

The QUALITOP cohort from France includes three historic and two prospective databases from Hospices Civils de Lyon (**Table 1**). The historic IMMUCARE ELDERLY cohort focused on clinical outcomes and irAEs after initiating ICI monotherapy or combination therapy between 2007 and 2019, with follow-up until late 2020. Data collected in the IMMUCARE BASE from 2019 in a clinical trial ('A Clinical and Biological Prospective Database of Patients Treated with Anticancer Immunotherapy and Follow-up of Their Immune-related Adverse Events irAE', registered NCT03989323 in clinicaltrial.gov) constitute the second historic cohort. This collected data for approximately 550 patients from the start of ICI treatment, irrespective of cancer type. Since August 2021, the study has included the QUALITOP quality of life questionnaires, demarcating the start of the prospective IMMUCARE BASE QUALITOP cohort. Earlier, in April 2021, the QoLD CART study began the prospective monitoring of HRQoL using the FACT-Lym for patients with diffuse large B-cell lymphoma receiving CAR T-cell therapy. Patients diagnosed with lymphoma who receive CAR T-cell therapy will be invited to a prospective QUALITOP cohort.

The Netherlands

We will include three historic and two prospective databases from the Netherlands. The OncoLifeS data biobank has collected data on clinical well-being and quality of life (assessed by EORTC-QLQ C30) since 2015 for patients with an oncological diagnosis treated in the University Medical Center Groningen.[29] Quality of life is monitored for 2 years after treatment and clinical outcomes are monitored continuously. We extracted additional data on irAEs for a historic cohort of approximately 500 patients with lung cancer who received ICIs and will use the same processes to collect the

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prospective data. Amsterdam University Medical Centers will lead the data collection for patients treated with CAR T-cell therapy in the Netherlands from January 2020, using data from the nationwide 'Follow that CAR' biobank initiated by the Dutch National CAR-T Tumor Board. This biobank has prospectively monitored clinical outcomes and quality of life, using the FACT-Lym, for patients with diffuse large B-cell lymphoma treated with CAR T-cell therapy. The historic cohort comprises approximately 40 patients, and the same process will be used to collect the prospective data. Lastly, the eQuiPe study collected data on quality of life for patients with advanced cancers in the Netherlands and is linked to the Netherlands Cancer Registry. The data from this study are included as a historic cohort.

Portugal

The Instituto Português de Oncologia in Lisboa invited patients diagnosed with lymphoma treated with CAR T-cell therapy or ICIs to participate in the prospective QUALITOP cohort from the end of 2021 onwards. No historical patient data are available.

Spain

The Hospital Clinic of Barcelona has asked patients treated for melanoma to consent to the inclusion of their data in the "Xarxa de Melanoma de Catalunya" database since 2016. This database allows participating centres to investigate phenotypic, genetic and disease evolution in patients, using biomaterials, including DNA, stored in the "Colecció de la Unitat de melanoma" (IDIBAPS registry code: R120904-090, National ISCIII registry code: C.0000334). Since January 2020, they have collected data on clinical well-being and quality of life (assessed by EORTC-QLQ C30) for patients with melanoma treated with ICIs. We have included approximately 50 patients in a historical melanoma cohort and will use the same process for the prospective data collection.

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Supplement 2: Overview of collected clinical data

All clinical data is manually extracted from patients electronic medical records. Data collected include, but are not limited to, the examples provided.

Domain	Examples
Baseline	
Patient demographics	Sex, month and year of birth, height
Cancer diagnosis	Cancer type (ICD-10), date of diagnosis, current stage (TNM/Lugano)
Past and current cancer treatment	Type of treatment (surgery, chemotherapy, targeted therapy, immunotherapy, radiotherapy), treatment line, start date, stop date, treatment medication, medication dose, number of cycles, best response, early treatment termination, reason for early treatment termination
Medical History	Relevant medical history (ICD-10) (e.g. cardiovascular diseases, neurological diseases, pulmonary diseases, diabetes, renal diseases, malignancies, auto-immune diseases), start date, end date
Current medication	medication type (according to Drug Ontology (DrOn), start date
Continuous monitoring	
Clinical examination	Date of examination, weight, temperature, heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, respiratory rate, ECOG performance status, response to treatment (RECIST/Lugano)
Blood analyses	Date of examination, CRP, glucose, creatinine, troponine, ASAT, ALAT, LDH, albumin, protein, sodium, potassium, leucocytes, erythrocytes, thrombocytes, neutrophils, eosinophils, lymphocytes, haemoglobin, TSH, FT4, cortisol
Adverse events	Adverse event type (CTCAE), adverse event grade (CTCAE), start date, end date, treatment

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6/7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7/8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-16
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9,11-16
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-16
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N.A.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	17-18
		(*b*) Describe any methods used to examine subgroups and interactions	N.A.
		(*c*) Explain how missing data were addressed	17-18
		(*d*) If applicable, explain how loss to follow-up was addressed	N.A.
		(*e*) Describe any sensitivity analyses	N.A.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N.A.
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N.A.
		(b) Indicate number of participants with missing data for each variable of interest	N.A.
		(c) Summarise follow-up time (eg, average and total amount)	N.A.
Outcome data	15*	Report numbers of outcome events or summary measures over time	N.A.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	N.A.

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		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N.A.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N.A.
Discussion			
Key results	18	Summarise key results with reference to study objectives	N.A.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N.A.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N.A.
Generalisability	21	Discuss the generalisability (external validity) of the study results	N.A.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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