Vincent Lau
Department of Critical Care Medicine (adult)
University of Alberta

22 July 2021

Dear Vincent,

Thank you for submitting your research proposal. The Executive Committee of The EuroQol Group Association ("the **Group**") has agreed to make available a budget of €39680 ("**Grant**") for your research project titled *"Validation of EQ-5D-5L in critical care (EuroQoL Working Groups Project Request for Proposal)"* on June 9th, 2021, as outlined in your project proposal, see appendix I ("**Project**"). This Grant is subject to your agreement to, and compliance with, the terms and conditions stated in this conditional project funding approval letter ("Conditional Grant Offer Letter") and its appendices.

As is the case with all proposals funded by EuroQol Research Foundation ("**the Foundation**"), the amount you requested for your accepted proposal will be made available subject to the following conditions:

i. Funding of all projects is conditional on adherence to certain principles that underpin the activities of the Foundation. Prominent among those is that all intellectual property rights (incl. copyright) in EuroQol instruments belongs to the Group and is managed by the Foundation to ensure the future financing of the Foundation.

ii. Any substantive changes or delays to your Project must be reported back to the Executive Committee immediately.

iii. Manuscripts must include the disclaimer statement that the views expressed by the authors in the publication do not necessarily reflect the views of the EuroQol Group.

iv. Of note, obtaining a grant from the EuroQol Research Foundation does not constitute a permission to use and/or modify EuroQol instruments. A license agreement, GTC or other applicable document(s) may be required by EuroQol, based on EuroQol's policy. The terms and conditions set out in the applicable document(s) shall apply to the use of the EuroQol instrument.

50% (€19840) of the budget will be made available to the research team when a signed copy of this letter and an invoice, making reference to **EQ Project 299-RA**, from your institute are received.

If you are **the direct recipient of the project budget**, then invoice submissions can be done electronically via our online portal: http://reimbursement-portal.euroqol.org. If you wish to submit an invoice **on behalf of another party**, please submit your invoice to accountspayable@euroqol.org. For any questions on invoicing and payments please contact finance@euroqol.org.

Note that as the Principal Investigator you are responsible for the study budget, so you need to keep track of invoicing. This requires that you provide a budget break down to the Foundation, and that

all invoices are sent with a letter of you confirming that tasks have been completed so far. Please use the **EQ project number**, see above, for all invoices.

A report should be provided on completion of the Project. To submit a report you need to log in to the project submission portal https://euroqol-proposals.grantplatform.com/ start a new submission and select 'Final report' as the category your submission. The remaining budget (€19840) will be transferred to your institution after signoff by the Executive Committee of your report and after confirming that the conditions stated above have all been met.

To accept this conditional grant offer, please have an authorised signatory sign and date a copy of this letter, and return to me.

Yours sincerely,

Elly Stolk,
For and on behalf of the EuroQol Research Foundation

By signing this letter, I confirm the agreement of Vincent Lau to the terms and conditions in this Conditional Grant Offer Letter and I warrant that I am authorised to enter into the Grant agreement and to bind and represent the Principal Investigator.

Signature: Z-Z LW

Date: July 26, 2021
Name: Vincent I. Lau
Title: Assistant Prof
Organization: University of Alberta Dept of Critical Care Medicine

Signature and details of EuroQol representative receiving signed copy

Signature: stolk@euroqol.org Digitaal ondertekend door stolk@euroqol.org Datum: 2021.07.23 15:59:54 +02'00'
Date:
Name: Elly Stolk
Title: Scientific Team Leader
Organization: EuroQol Research Foundation

Appendix
I: Study proposal, as agreed by the EQ Executive Committee
II: General terms and conditions EuroQol Funding v1.0

Vincent Lau
Department of Critical Care Medicine (adult)
University of Alberta

22 July 2021

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To accept this conditional grant offer, please have an authorised signatory sign and date a copy of this letter, and return to me.

Yours sincerely,

Elly Stolk,
For and on behalf of the EuroQol Research Foundation

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Signature:

Date: _____
Name: _____
Title: _____
Organization: _____

Signature and details of EuroQol representative receiving signed copy

Signature:
Date: _____
Name: Elly Stolk
Title: Scientific Team Leader
Organization: EuroQol Research Foundation

Appendix
I: Study proposal, as agreed by the EQ Executive Committee
II: General terms and conditions EuroQol Funding v1.0

Validation of EQ-5D-5L in critical care

QwdqArjz

Submission details

Full Title

Validation of EQ-5D-5L in critical care (EuroQoL Working Groups Project Request for Proposal)

Abstract.
provide a brief summary of your research proposal, including the aims and general methods proposed. Provide enough information to enable the reader to understand what will be done, and how. Please note that the abstract will be posted on EuroQol website for successful applications.

Critical care research typically reports outcomes which are patient-important, specifically mortality and morbidity. However, healthcare providers, patients and families are not only interested in patient survival, but also health-related quality-of-life (HRQoL) before, during and after critical care.
Prior critical care research has not routinely described patient-reported outcomes like HRQoL. Patient-reported health utility can be elicited using various indirect, generic preference-based value measures. The most common generic method is the EQ-5D-5L. It has advantages including accuracy at low utilities compared to other HRQoL tools, no licensing fee for non-commercial use, and a built-in visual analog scale (VAS) for self-rating a patient's health status. It's more user-friendly than other instruments (e.g. SF-36). EQ-5D-5L has proxy instruments in addition to patient-reported instruments. Measuring baseline HRQoL in critically ill patients can be used to predict potential downstream outcomes. Prior research has shown that low HRQoL prior to critical care admission is associated with a grim prognosis in terms of survival, and leads to deterioration in the HRQoL post-discharge (23–28).
The EQ-5D-5L has not been previously validated in critical care. Patient-reported outcomes like HRQoL and quality-adjusted life-years (QALYs) are being increasing used and recognized as important endpoints to measure. With more patients surviving their critical illness, documenting ICU survivors HRQoL (patient-reported psycho-social and physical functional domains) becomes important in its own right.
Therefore, the objectives of this proposal are to: (1) validate the EQ-5D-5L-5L in the critical care setting; and (2) compare proxy and self-complete versions of the EQ-5D-5L-5L in critically ill patients.

Budget requested from EuroQol (euro)	39680
Are you receiving co-funding or in kind support from another organisation?	no
Relevant Working Group(s)	✓ Descriptive systems working group ✓ Valuation working group ✓ Large-scale applications working group

Research strategy

Details of your research plan

(1) Background of the problem;
Critical care research has typically reported on outcomes which are patient-important, specifically mortality and morbidity. However, healthcare providers, patients and families are not only interested in patient survival, but also health-related quality-of-life (HRQoL) before, during and after critical care. Although medical technology has the ability to sustain life, often intensive care unit (ICU) survivors are left in poor health states with impaired HRQoL post-ICU (7), with loss of functional autonomy and dependence on the healthcare system (8). Physicians routinely recommend withdrawing or withholding life-sustaining therapies based on patient prognosis or if their perceived HRQoL is expected to be poor (7), as being on life support could be considered a "fate worse than death" (9).
Prior critical care research has not routinely described patient-reported outcomes like HRQoL, despite the importance to patients themselves and their families. Knowing patient's quality-of-life before, during and after ICU stay is slowly being recognized as important measures to ascertain from patients. A few HRQoL instruments have been used in critical care setting (e.g. SF-36, HUI-3, World Health Organization Disability Assessment Schedule [WHODAS]) (13, 14, 15). For example, the Short Form-36 has been used previously in the critical care setting (13–17), and was previously validated (18), but not against any other known illness severity scores or other HRQoL measures (18, 19).
In this regard, there are potential benefits to measuring HRQoL in critically ill patients, specifically the EQ-5D-5L. First, the EQ-5D-5L is shorter and simpler than other instruments like the SF-36, which has limitations including its length and tendency for patients not to be able to complete it (20). Second, the EQ-5D-5L has the ability to use a proxy instrument in addition to patient-reported instruments. Third, measuring baseline HRQoL in critically ill patients can be used to predict potential downstream outcomes. Prior research has shown that low HRQoL prior to critical care admission is associated with a grim prognosis in terms of survival, and leads to deterioration in the QoL (in the short-, mid- and long-term) after discharge (1–6). Finally, the critical care environment could be a setting where low health utilities may be experienced and realized, where "fates worse than death" would be important to be measured, especially alongside the EQ-VAS self-reporting tool. Validating the EQ-5D-5L would be important to its continued and potential increase in utilization of this tool in the critical care population, and also increase overall measurement of HRQoL and patient-reported outcomes.

(2) Aim of the research;
Therefore, the objectives of this proposal are to: (1) validate the EQ-5D-5L in the critical care setting in Canada; and (2) compare the proxy and patient-reported, self-completed versions of the EQ-5D-5L in critically ill patients.

(3) Proposed methods;
Design:
Type of study: Prospective cohort study (across Canada, with varied geographical and socio-demographic distribution) – cross-sectional and longitudinal components
Sample Size: No guidelines on sample size requirements for instrument validation. However, general recommendation is to have a minimum of 100 respondents (21).
Target Population: all, adult (>18 years old) ICU patients
Stratified by:

- Case-mix (medical/surgical/trauma)
- illness severity (e.g. Sequential Organ Failure Assessment [SOFA])
- clinical scores (e.g. Clinical Frailty Score [CFS])
- length of ICU stay
- duration of mechanical ventilation
- duration of vasopressor utilization
  Instruments to be used:
  Psychometric analyses: guidelines by Scientific Advisory Committee of the Medical Outcomes Trust (22)
- EQ-5D-5L & EQ-5D-5L Proxy
- SF-12
- Construct Validity
  • Convergent and divergent validity: extent to which a measure corresponds to an accurate or previously validated measures of the same concept
  o Examining the correlations between scores of EQ-5D-5L, EQ-VAS, SF-12 Physical (PHC) and Mental health composite

(MHC) scores.
 Evaluate convergent validity: determine if there are strong correlations between similar items/domains in EQ and SF-12 (e.g. those measuring physical functions, those measuring mental functions)
 Evaluate divergent validity: measure correlation between items/domains measuring different construct, EQ walking vs SF-12 mental function. We hypothesize a weak correlation among dissimilar constructs.

o Spearman's rank correlation coefficients calculations:
 < 0.30 weak correlation
 0.30-0.50 moderate correlation
 > 0.50 strong correlation
• Known group validity (distinct group discrimination with EQ-5D-5L): process whereby the measure is correlated with preconceived differences, which may be clinically established or theoretical constructs
o Ability of EQ-5D-5L to discriminate between health states of pre-defined groups over time
• Content validity: extent to which an outcome measure covers the range or diversity of intended measurement (e.g. avoidance of floor or ceiling effects)
Comparisons/correlations with illness severity scores in critical care (test known group validity):
• Sequential Organ Failure Assessment [SOFA]: (cardiovascular, respiratory, hepatic, renal, hematologic, neurologic)
o Score is calculated on admission and every 24 hours until discharge using the worst parameters measured during the prior 24 hours.
o Scores can be used in a number of ways: As individual scores for each organ to determine progression of organ dysfunction.
o As the sum of scores on one single ICU day
• Multi-organ dysfunction Score (MODS)/Acute Physiology And Chronic Health Evaluation (APACHE) II – only on admission
• Test known group validity: use measures to define clinically distinct groups, and see if EQ-5D show correlations or differences
Measurement time points:
• Baseline (2 weeks prior to admission) – proxy (when patient is incapacitated) EQ-5D-5L alongside SF-12
• Admission – patient or proxy (if patient is incapacitated) EQ-5D-5L alongside SF-12
• Discharge – patient or proxy (if patient is incapacitated or dead) EQ-5D-5L alongside SF-12

Analysis:
• Socio-demographics will be described using number and percentage for categorical variables such as diabetes, and the median (with interquartile range [IQR]) for continuous variables such as age. Range, % of negative health utility/HRQoL scores and % ceiling (maximum)/floor (minimum) scores.
• Categorical data will be compared using a Chi-square test, unless the expected cell frequency condition failed, in which the Fisher's exact test will be used.
• Continuous data will be compared using paired t-tests if the distribution was approximately normal or the Wilcoxon matched-pairs signed-ranks test if the distribution is skewed.
• Associations among the HRQOL instruments (EQ-5D-5L vs. SF-12) will be quantified using Spearman's rank correlations.
• The EQ-5D-5L general health scores will be compared between the predefined groups to assess construct validity (t-tests).
• All tests will be two-sided and of statistical significance at an alpha level of 0.05.
• Hypothesis testing to examine the construct validity of predetermined groups will be one-sided.
• Our analyses will be performed using SPSS, SAS.

(4) What will the EuroQol Group learn/gain by funding this research proposal
Tables and figures may be attached.

Although there has been an increase in the utilization of these various health utility metrics, many of the aforementioned tools have not been rigorously validated in the critical care setting (18), despite their prior use (11, 23, 24). Validation of these tools would be important for validity and applicability across the heterogeneous disease states and wide range of interventions that are provided in a critical care setting. Furthermore, patient-reported outcomes like HRQoL and quality-adjusted life-years (QALYs) are being increasing recognized as important endpoints to measure, in addition to mortality and morbidity for critically ill patients. With more patients surviving their critical illness, documenting ICU survivors HRQoL

becomes important in its own right as to properly describe a patient's experience from their functional and mental health domains.
There are some methodologic barriers to measuring HRQoL in the critical care setting. For the issue of missing HRQoL, potential solutions include data imputation, assigning fixed unconscious health utility states or asking patient surrogates or health care professionals to estimate HRQoL (25–27). As many patients are incapacitated during their ICU admission, proxy HRQoL data collection from surrogate decision makers or caregivers may be required (28). Methods to circumvent this have been to use longitudinal population surveys that capture HRQoL pre- and post-hospitalization stratified by critical illness (29–32). However, we encourage that HRQoL be collected directly from patients, to ensure we are listening to them by capturing patient-centered values and self-reported well-being whenever possible. Researchers may need to wait until critical care patients are well enough to participate in patient-reported outcomes (PROs), with potential issues of recall or survivorship bias (33), and some patients may not return to baseline or survive their illness. One aim would be to verify surrogate/proxy HRQoL measurements alongside patient-reported HRQoL.

Please list the deliverables of your research and describe their value to EuroQol

Deliverables:

- Conference presentation (at least 1)
- Manuscripts (at least 2 papers):
  o Describe validation of:
  - EQ-5D-5L in critical care (patient)
  - EQ-5D-5L in critical care (proxy)
- Value to EuroQol:
  o Increase the validation and utilization of EQ-5D-5L/proxy instruments in an area (critical care) where there will likely be lower described health utilities and potentially "fates worse than death" (to further demonstrate the importance of the EQ-VAS alongside the EQ-5D-5L)

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Proposed start date	2021-09-01
Duration of your project (in months)	24
Does your research require the development of a modified or new version of an EQ instrument (changed wording, bolt ons, new language version, new mode of administration)?	✓ no, all required versions are available

Please describe the timelines of your research. If you prefer to upload this as an attachment, please indicate that in the field

- April – September 2021: EuroQol proposal grant procurement, finalization of research ethics board approval, institutional approvals
- September 2021 – April 2023: Validation study recruitment
- April 2023-September 2023: Analysis and publication of validation study

Is this proposal part of another investigation, funded by EuroQol or another party?

No

how will confidentiality and security of the data be assured?

Personal data will not be collected. All data will be de-identified prior to analysis. All data will be housed in encrypted files and on password-protected computers behind institutional firewalls at the University of Alberta.
We are applying for Research Ethics Board approval, given that we are still requesting de-identified data of the patients who undergo this protocol. Computer databases and medical records will be queried for patient baseline demographics and clinical characteristics. We will apply for research ethics board review for access to institutional databases to be able to publish our findings.

Ethics approval status	pending

Notes about ethics approval

Submission to University of Alberta Research Ethics Board:

- registration # Pro 00110111

Budget specification (in Euro)

XLSX	EQ-5D Validation Critical... (17 KiB download)

You can upload the CVs of project team members here, all combined in a single file (.doc or .pdf)

PDF	Combined CVs.pdf (2.3 MiB download)

Project team

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Log in to euroqol-proposals.grantplatform.com to see complete submission attachments.

***The General Terms & Conditions EuroQol funding of STICHTING EUROQOL RESEARCH FOUNDATION**, also trading as **EUROQOL RESEARCH FOUNDATION**, a registered charity incorporated under the laws of The Netherlands, having its registered office in Rotterdam, and its principal place of business in (3068 AV) Rotterdam at the Marten Meesweg 107, The Netherlands* (hereinafter '**EuroQol**') is accepted by signing the letter for approval for the funding of the EQ Project (hereinafter: "**Approval Letter**").

Applicant understands and agrees that the conditions in these General Terms and Conditions EQ Project (hereinafter: "**GTC**") will apply.

Article 1 – Scope

a) Funding does not constitute a permission to use and/or modify EuroQol instruments. A license agreement, GTC or other applicable agreement(s) may be required by EuroQol, based on the user license policy. The terms and conditions set out in the applicable agreement(s) shall apply to the use of the EuroQol instrument.

b) If one or more provisions in these GTC are partially invalid or destroyed, these GTC shall at all times remain applicable to the remainder. If one or more provisions are invalid or destroyed, EuroQol and Applicant will agree on new reasonable terms to replace the invalid or destroyed terms.

Article 2 - Definitions

The definitions stated below have the following meaning in the context of the standard terms and conditions set out in these GTC.

a) **Approval Letter** is the letter signed for approval for the initiation of the EQ Project;

b) **IP Rights** means copyrights, neighbouring rights, patents, design rights, trademarks, service marks, database rights, know-how, trade or business names, rights in confidential information and all other IP rights and rights of a similar nature, whether registered or unregistered and wherever in the world such rights arise;

c) **Applicant** means the person who requests the funding;

d) **EQ Project** is the project which EuroQol will fund after signing the Approval Letter.

Article 3 - Confidentiality

a) EuroQol will keep confidential all EQ Project information received from Applicant.

b) Applicant will not disclose confidential information to third parties not involved in the EQ Project.

Article 4 - IP Rights

a) All IP Rights in EuroQol instrument(s) (incl. but not limited to minor/major change of wording), enhancements, improvements, updates, new versions, derivative works or (new) translations) belong to EuroQol and are managed by EuroQol to ensure the future financing of EuroQol.

b) Within **thirty (30) days** after a request of EuroQol, Applicant shall provide all co-operation and assistance to ensure that the IP Rights are transferred and assigned to EuroQol, including, but not limited to the immediate execution or procurement of all such documents necessary to assign and transfer the IP Rights in and to EuroQol based on EuroQol's applicable IP Rights policy. EuroQol shall be the final arbiter to decide which documents will be needed. Once EuroQol confirms in writing that the IP Rights assignment and transfer is complete, the IP Rights transfer and assignment can be considered final.

c) These GTC do not grant EuroQol or Applicant rights to or interest in each others background IP Rights. For avoidance of doubt, all IP Rights, in, or in connection with EuroQol instruments are vested and shall remain vested in the Group.

d) Applicant declares and warrants the following;

i. Applicant will not claim IP Rights from the Receiver in connection with the assignment and transfer of the IP Rights;

ii. Applicant will not claim (financial) compensation from the Receiver in connection with the assignment and transfer of the IP Rights;

iii. Applicant will not provide permission to any third party for the use of EuroQol instruments;

iv. Applicant will not distribute or provide EuroQol instruments to third parties;

v. Applicant will not transfer IP Rights in or in connection with the EuroQol instrument to any third party; and

vi. Applicant will not make agreements, arrangements and understandings, whether in writing or oral with third parties related to EuroQol instruments, without the prior written permission of EuroQol.

Article 5 - Budget

EuroQol is entitled to retain the transfer of the remaining budget in the following events:

i. Applicant infringes EuroQol's IP Rights policy; and/or

ii. Applicant does not comply with EuroQol's user policy; and/or

iii. Non-compliance with funding conditions.

Article 6 - Liability

a) EuroQol shall not be responsible nor liable for the EQ Project, except in case of damage resulting from gross negligence or willful misconduct by EuroQol.

Article 7 - Dispute Resolution and Governing Law

a) These GTC shall be governed by, and construed in accordance with, the laws of the Netherlands.

b) In the event of a dispute arising out or in connection with these GTC, EuroQol and Applicant shall strive for an amicable settlement.

c) If amicable settlement is not achieved, the dispute shall be finally settled by the competent court in Rotterdam, the Netherlands.

d) Notwithstanding the foregoing, nothing shall affect the right to seek an immediate remedy of an injunction, specific performance or similar court order to enforce the defaulting party's obligations.