Citizens Petition to the Food and Drug Administration

Assessing Changes to the Patient's Quality of Life (QoL) is Integral to Interpreting the Efficacy of Study Treatments for Cancer

"Improved reporting of PROs (Patient Reported Outcomes) will enable accurate interpretation of evidence to inform patient choice, aid clinical decision making, and inform health policy." [1]

"PROs are reports of the status of a patient's health condition that come directly from the patient, without interpretation of the patient's response by a clinician or anyone else." [2]

This letter is a petition to the Food and Drug Administration (FDA). We are requesting that the FDA require the assessment of changes to the participant's quality of life (QoL) in comparison studies, particularly for studies that have chosen surrogates for efficacy (such as Progression Free Survival (PFS)) as the primary endpoint. Further we request setting standards for the capture and reporting of changes to QoL and related PROs from baseline in order to aid regulatory and clinical decision-making.

Some important effects of treatments, such as fatigue, nausea, anxiety, and pain, can only be reported by the patient -- cannot be measured with laboratory tests. Some may be present before treatment, or emerge as a side effect of therapy.[3] These effects can be amplified for treatments given continuously until disease progression or until the side effects cannot be managed. Some of these effects may persist or resolve when the treatment is stopped.

Bishal Gyawali, and colleagues have called for greater clarity and transparency in reporting the patient experiences – finding that "studies of cancer drugs often use terms that downplay the seriousness of adverse events:"

> *The clinical trial report of ribociclib, a drug for breast cancer, mentions in its discussion that "Most patients had an acceptable adverse-event profile."1 A report of a trial of liposomal irinotecan in pancreatic cancer states in the concluding paragraph that it "has a manageable and mostly reversible safety profile."2 And a trial of tasquinimod in patients with prostate cancer reports "the tolerability was good overall."3*
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> *All three of these studies were published in top medical journals. Naturally, readers would take these statements to be true. However, a look at the data for adverse events doesn't paint as good a picture. In the first study, more than twice as many patients in the ribociclib arm as in the control arm experienced severe (grade 3 or higher) adverse events (271/334 v 108/330).1 The*

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[1] *Patient-reported outcomes in randomized clinical trials: development of ISOQoL reporting standards | Qual Life Res. 2013; 22(6): 1161–1175. Published online 2012 Sep 18. doi: 10.1007/s11136-012-0252-1 http://bit.ly/2Uo3QqU*

[2] *Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms | Clinical Cancer Research Paul G. Kluetz, Ashley Slagle, Elektra J. Papadopoulos, Laura Lee Johnson, Martha Donoghue, Virginia E. Kwitkowski, Wen-Hung Chen, Rajeshwari Sridhara, Ann T. Farrell, Patricia Keegan, Geoffrey Kim and Richard Pazdur http://bit.ly/2UidzuY*

[3] *Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials Patient. 2015; 8(4): 301–309. http://bit.ly/2NwnR8N*

difference in treatment related serious adverse events (leading to death, life threatening condition, hospital admission or prolonged admission, disability or permanent damage, congenital anomaly or birth defect, or that required medical or surgical intervention to prevent one of the other outcomes4) was nearly five times higher (25 v 5).

The goal of medical research is to provide relief from pain and suffering - and to restore our health by controlling or eliminating disease. Mary, with her energy restored, can now return to work. Joe, no longer debilitated by pain, can laugh with and encourage his kids. Ideally, following the new treatment, Mary and Joe may also live longer.

Dr. Judith Karp writes:

"Quality of life (QoL) is critical to any response (or even without achieving so-called "objective response") -- and even if there is no quantitative improvement in survival, having a life that has quality is paramount to what we are supposed to be trying to accomplish! This has always been one of my major issues with bone marrow transplant -- chronic GVHD is no way to live. Or, in another vein, mere existence really is not fun (the "old man river syndrome:" tired of livin' and scared of dyin')."

The unfiltered capture of the patient experience, before, during, and after treatment, provides essential unbiased information helping to determine if the study treatment deserves marketing approval and if so, what supportive care and information about the treatment must be provided to the patient as part of usual care.

Of equal importance is how QoL and related PROs are reported in clinicaltrials.gov and in medical journals. These reports must provide a clear context for public and regulatory understanding of how PROs compare and change during the course of study treatments and during follow up.

It might begin by describing the median age of the study participants and how these compare with the age of patients afflicted with the disease. It might cite the median QoL scores for the undiagnosed population. It should provide the baseline QoL scores for each arm of the study and what percentage had extremely poor baseline QoL (scores 1.5-2) … which might have prognostic significance. [4]

Example of how it might be done:
Side-by-side reporting of changes to the participant's QoL from baseline:

QoL: the patient's assessment of his or her overall well-being influenced by physical, mental, social, and financial stresses including the symptoms of the disease and the possible long- and short-term side effects of treatments.

Baseline QoL	**Arm A:** n = 100	**Arm B:** n = 100
QoL baseline *0 as bad as it can be, 10 Excellent*	5	5
Impaired QoL (>8)	10%	4%
Mean QoL (+ or - change from baseline)	**Arm A:**	**Arm B:**

[4] *Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials - ScienceDirect | Chantal Quinten, MSc Corneel Coens, MSc Murielle Mauer, PhD Sylvie Comte, MD Prof Mirjam AG Sprangers, PhD Prof Charles Cleeland, PhD et al.* http://bit.ly/2CN6kFn

On-study QoL	4.5 (-.5)	6 (+1)
Follow-up QoL	5 (0)	7 (+2)
For Impaired-QoL at baseline	2 (0)	2 (0)
For Impaired-QoL during follow up	3 (+1)	2 (0)
At 1-year follow-up – all responses:	4 (-1)	6 (+1)
For complete responders	30% 7 (+2)	20% 7 (+2)
For partial responders	30% 4 (-1)	40% 7 (+2)
Stable disease	10% 3 (-2)	20% 5 (0)
Refractory to study treatment	30% 3 (-2)	20% 4 (-1)
At 2-year follow-up – all responses:	4 (-1)	6 (+1)
When available provide the mean QoL for the undiagnosed population for this age group using the same PRO instrument.		
Mean PROs (+ or - change from baseline)	**Arm A:**	**Arm b:**
Fatigue* baseline *1 is poor, 10 outstanding, *endpoint*	5	5
On-study Fatigue	4.5 (-.5)	6 (+1)
Follow-up Fatigue 1 and 2 years	4.5 (-.5) | 4.5 (-.5)	6 (+1) | 6 (+1)

The full PRO report should call attention to the PROs of interest -- the known side effects of the study treatments, such as fatigue, pain, insomnia, and nausea. The report ought to show the median baseline scores for each of these, along with any hypothesis or expectation of what may improve or get worse during treatments and/or how these may be addressed with supportive care.

The PRO report should conclude with a table listing the baseline PROs and QoL scores for each study arm, with a column indicating if any could be treatment- or disease-related, or both.

PRO comparisons and changes from baseline might use the format above. To assess for confounders, baseline and changes to key domains for QoL should be captured and reported: emotional, physical, social, financial, and spiritual well-being,

Of particular concern is that we are often basing marketing approval on time to progression without knowing if the study treatment improves how well or long the patients live. With accelerated approvals the patients with modest financial resources may be mortgaging the future of their families to gain access to the agents which can have very high out of pocket costs.

Do improvements in PFS inherently improve the well-being of patients? The evidence to date does not support this perspective.[5] The available evidence is also limited by reporting bias – the large number of studies that have not captured and or reported QoL data. Consider that some types of cancer can be asymptomatic at relapse, and some effects of treatment can persist and impair QoL beyond the completion of the study treatment. Some side effects may also limit the potential to receive or benefit from subsequent treatment. Thus, we can't assume that improvement in PFS will translate to living longer or better -- we need to measure QoL specifically.

We may also find that study treatments that delay relapse without impairing QoL are more likely to help patients to live longer. With no impairment or improvement to QoL regulators can have higher confidence that their decision to grant a conditional marketing approval of a study drug

[5] Association between progression-free survival and patients' quality of life in cancer clinical trials. Hwang TJ1,2, Gyawali B1,2. | Int J Cancer. 2019 Apr http://bit.ly/2ti7R17

based on a surrogate endpoint is truly reasonable. *See also "Limitations of PFS as predictive of clinical benefit" in the attachment.*

QoL Is Integral to Assessing Efficacy

In summary, living longer with improved QoL is the ideal outcome for patients. Comparing PROs can help to tell us if a gain in survival or delay of relapse is worth the price - impairment of QoL or, conversely, if it was achieved with little or no impairment of the patient's well-being. The latter might support the use of surrogates for benefit; the former may give pause and call for longer follow up.

Reported directly by the patient, PROs provide unfiltered changes to the patient's quality of life that can be impaired by fatigue, pain, nausea, inability to sleep -- that may be misinterpreted, abbreviated, or understated in summary journal reporting - such as: the treatment was "well tolerated." [6]

Capturing baseline and on-treatment and post-treatment PROs may help to identify disease- versus treatment-related side effects of the compared interventions. Baseline QoL scores appear to have prognostic significance, which can further direct supportive care. A recent comparative study found that the use of electronic PROs (ePROs) decreased emergency room use and improved survival!

With standard adverse event (AE) assessments can we tell if the fatigue was present before the treatment? Can we assess if the fatigue is treatment- or disease-related? Can we know if there's a relationship of the symptom to the response to treatment? Can we know if the experience and sense of well-being persists when treatment is discontinued?

The importance of patient reported outcomes increases when the treatments require maintenance or continuous use of drugs to induce and maintain a response. Consider the potential on-study burden to the patient for a treatment having side effects that requires two years of continuous treatment on a daily basis to achieve an improvement in PFS of months.

The standard use of PROs will improve the patient experience and increase public trust in the reporting of results. The use of electronic instruments (ePROs) promises to make the capture and reporting completely automated, requiring little to no extra time of the study team to generate standardized reports.

Finally, the standardization of PRO elements and reporting will foster more objective comparisons of study population and outcomes. On-treatment ePROs appear to decrease the risk to study participants – helping to identify safety issues earlier, direct supportive care and potentially improve survival [7].

Large randomized trials are hard to get done and more challenging to ever repeat. Thus, we owe it to the patients to keep them as safe as possible and to optimize the knowledge gained from each clinical trial. There seems no just reason to routinely exclude from the reporting of clinical trial results the unfiltered experience of the patient - reported in a manner that promotes public

6 Reporting harms more transparently in trials of cancer drugs | The BMJ 2018 | Bishal Gyawali, http://bit.ly/2BUnArQ

7 Electronic Patient-Reported Symptom Monitoring Associated With Increased Survival Among Patients with Metastatic Cancer - For The Media - JAMA Network | Ethan Basch, M.D http://bit.ly/2XlWB1o

and professional understanding of clinical research. Based on the low rate of QoL assessments and poor QoL reporting in randomized clinical trials, FDA help is needed.[8] We cannot expect the drug sponsors to voluntarily add to the scope of what is studied.

Actions Requested:

For the reasons explained in more detail above, we (the undersigned) respectfully requests that FDA take the following actions:

- Provide guidance to clinical trialists, drug sponsors, and Institutional review boards regarding the need to capture and compare changes to the participants QoL and related patient reported outcomes.

- Help to set standards for PRO reporting, beginning with ClinicalTrials.gov, so that what is reported can be understood and used to interpret the results and to guide clinical practice and better-informed patient choice.

- Require or strongly suggest to the sponsors of clinical trials that comparative studies include QoL assessments – particularly when the primary endpoint is a surrogate for clinical benefit.

You can show your support for this petition by providing your name and zip code here: Petition Form

Sincerely,

Karl Schwartz
Patient advocate, caregiver / Formerly: President of Patients Against Lymphoma, FDA patient representative, CIRB member – adult early phase, NCI Steering committee for lymphoma and co-chair Patient Advocate committee.

Additional Background attached:

How is Clinical Benefit defined? | What are the limitations of PFS as predictive of clinical benefit?
How are QoL and PRO defined? | How often and well is QoL reported in Lymphoma / CLL studies?
Assessing changes to QoL with efficacy endpoints | Assessing the Whole Patient

The names and citizens who endorse this petition with optional comments.

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Additional Background

How is Clinical Benefit defined? | What are the limitations of PFS as predictive of clinical benefit?

How are QoL and PRO defined? | How often and well is QoL reported in Lymphoma / CLL studies?

Assessing changes to QoL with efficacy endpoints | Assessing the Whole Patient

How is Clinical Benefit defined?

The goal of clinical research is to test therapies to assess which provide clinical benefit - which allow the patients (on average) to live better or longer.

Living better**:** assessing which treatment diminishes patient suffering / improves their quality of life can be challenging. The compared protocols may have different schedules, durations of treatment, and types of toxicities. The side effects of one therapy may be acute in one phase, but then much less than the other approach in another phase of the protocol.

Living longer: Assessing which treatment extends life can require very long follow up of the study participants. The assessment can be confounded by subsequent therapy
(was it the study treatment or the next treatments that made the difference?).

Is it desirable to extend life by months or years if the patients endure daily suffering?
Living better is integral to assessing the value of living longer.

Because assessing OS differences is challenging, surrogates that may predict for improvements in how long the patients live are often used. (such as PFS, complete response rates, delays in relapse). Surrogate endpoints have limitations that are important for the public and medical teams to understand.

The limitations of PFS as predictive of clinical benefit

The word "Survival" in PFS is misleading. An improvement in PFS does not always (and frequently doesn't) predict that patients will live longer.

PFS is a *composite* endpoint -- one thing that measure two kinds of events.
The progression and relapse events often outnumber death events in comparison trials.
Otherwise there would be a survival difference with no need to compare differences in PFS.

It counts:

1) relapse or progression of disease measured from the start of treatment

2) death from any cause.

PFS is used to estimate benefit (a surrogate for living longer) when it's not feasible or practical to compare how long the participants live.

Some investigators maintain that an improvement in PFS inherently improves QoL. But this needs to demonstrated not asserted. Some types of cancer can be asymptomatic at relapse, and

some effects of treatment can persist and impair QoL beyond the completion of the study treatment. Some side effects may also limit the potential to receive or benefit from subsequent treatment.

Regulators consider the magnitude of the difference in PFS, but also the toxicities. By including QoL and related PROS, regulators and patients can also better understand the impact on how well patients live while on treatment and during the follow-up period. In short, side effects (known and unknown, some long term) can offset PFS gains. Further the trend for developing drugs given on a continuous (often daily) basis until progression or until unacceptable toxicity increases the need to better account for the impacts on the patient's quality of life.

How often and well is QoL reported in Lymphoma / CLL studies?

Few Randomized Trials report QoL and the *reporting appears to be poor (often no baseline changes reported, difficult to read, and understand) and lacking in standards* when done for lymphoma and CLL:

Search of ClinicalTrials.gov Results including QoL assessments (date: 2/4/19):

11% of completed Phase 3 Lymphoma and CLL have assessed QoL **10%** have reported Results.

277 studies With or Without Results and QoL assessment http://bit.ly/2GajYG2

57 (21%) With or Without Results | that include QoL assessment http://bit.ly/2UzaSpk

30 (11%) Without Results | that include QoL assessment http://bit.ly/2HQ018N

27 (10%) With Results that include QoL assessment http://bit.ly/2UEL3E9

How are QoL and PROs defined?

From "The Emerging Patient Role in Toxicity Reporting... http://bit.ly/2RB0CuX

> "The more subjective a symptom is, the less likely a professional staff member is to detect it or grade it accurately. This means that oncology care providers often under-appreciate patients' symptoms at baseline when they enter a trial; when a symptom is later reported, it is not always clear whether it was present at baseline or emerged during treatment. It also means that oncologists miss many of the symptoms that subsequently develop. As a result, they lose precision in the measurement of toxicities in trials and have an incomplete picture of the patient experience when balancing risks with benefits.

QoL is the overall well-being of the patient reported by the patient - along with patient reported outcomes (PROs) *"PROs are reports of the status of a patient's health condition that come*

directly from the patient, without interpretation of the patient's response by a clinician or anyone else."

Baseline QoL and PROs -- particularly if the instruments and reporting are standardized:

* Can help determine if the study arms are balanced.

* Can inform about which emerging symptoms are disease- versus treatment-related.

* Can help to compare populations across different studies and interpret those outcomes --

* Can assess aggregate changes to QoL within and across study groups.

* Changes from baseline can direct timely supportive care or services to individual patients - helping them to stay on study and out of the emergency room.

Assessing changes to QoL with efficacy endpoints

Optimal benefit is when the patients live longer and better.

Relative to the control, the study intervention can:	Assessment
1. **Improve OS AND QoL**	Optimal benefit improving how well and long patients live.
2. Improve OS but NOT QoL	Impaired QoL informs clinicians and patients about tradeoffs, the cost of living longer.
3. Improve QoL only (single endpoint)	QoL benefit: patient lives with less suffering. Extends or decreases life? unknown.
4. **Improve PFS AND QoL** When both endpoints are met, is PFS more likely to predict OS?	QoL benefit proven: patients live with less suffering. (benefit) That study treatment extends life still uncertain, but seems more plausible.
5. Improve PFS without impairing QoL	Patient well-being the same That study treatment extends life seems plausible by is not certain until follow up.
6. Improve PFS but impairs QoL Hypothesis: PFS improvement that impairs QoL is less likely to predict OS.	Patient well-being impaired by what degree and for how long? Is it reversible?

	That study treatment extends life seems much less certain until follow up.
7. Improve PFS without assessing QoL *Is the study design unethical?* Is it reasonable to grant accelerated (conditional) approval?	Unknown impact on QoL: may increase, decrease or not change patient suffering. That study treatment extends life seems much less certain until follow up.

Assessing the whole patient with QoL

In addition to the underlying disease and side effects of treatment, stresses at home may affect the overall well-being of the patient: such as from the death of a loved one, concerns for a child, financial losses, lack of family support.

Questions to discover these confounding effects might be given separately on a subsequent day to relieve concerns about time to complete the questionnaire.

It's my deeply-felt impression that patients' welcome questions about their well-being and needs. Further, the understanding the whole patient enhanced by such question can help to guide supportive care which may help the participants living with "distal" stressors to remain on the study.

> *"The use of HRQoL (Health-related QoL) as a primary objective in cancer trials is further complicated by the need to measure domains considered distal from the effect of the drug on the patient and the patient's disease, such as social and family well-being, to completely capture this broad concept.*
>
> *Although questions addressing social and family well-being are important to patients and contribute to HRQoL, many non–drug-related contributors to social and family status can confound existing HRQoL measures. These issues may make an HRQoL endpoint less sensitive to the positive or negative effects of an investigational therapy on the patient." (Kluetz, Pazdur et al.)*