

PATIENT-REPORTED OUTCOMES: CAN THEIR USE IN OBSERVATIONAL ("REAL-WORLD") RESEARCH BE CONSIDERED INTERVENTIONAL?

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Issues Panel – Session 4



Some definitions

Patient-reported Outcome (PRO)

- A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else (FDA, 2009)

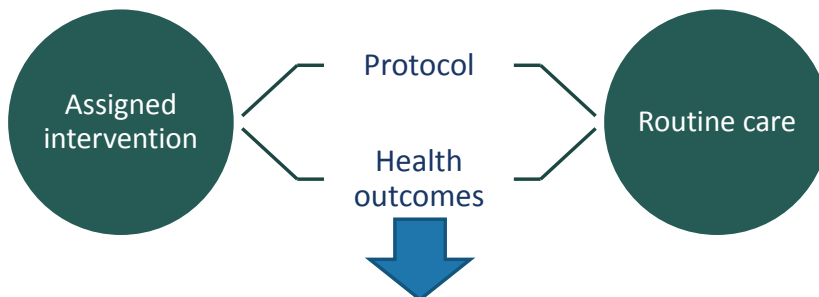
Observational studies

- A study that provides estimates and examines associations of events in their natural settings without recourse to experimental intervention (Mann, 2003)
 - Testing and interventions are decided within the course of usual care by the HCP team
 - Typical standards of care offered
 - Intended to ascertain effectiveness (and real-world safety) rather than efficacy

Interventional vs observational study

Interventional Study

Observational Study



Opportunity for collection of data that informs understanding the participants reality of living with the disease, condition, and/or health state



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How observational data compliments RCT data



pharma, regulators, payers, HCPs, patients



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Why collect PROs in observational research

PROs best measured in RCTs

PROs best measured in obs. studies



What is the debate?

- **Can PRO data can be collected in the “real world” without impacting on participant behavior?**
 - Duke University:
 - When PRO collection is aligned with clinical care, the information collected can be used in real time to triage patients, for quality monitoring, to trigger interventions and education, or for research.
 - These uses ... may help engage patients in their own health care over time and ultimately inform and improve evidence-based patient care
 - Observational research, by its definition must be non-interventional
 - PROs are not an intervention per se, but
 - PROs are not part of routine clinical care
 - PROs ask people to consider aspects of their lives that they may otherwise not

Speakers



A European
perspective

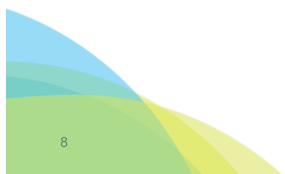


A US
perspective



Tasks

- Is there a regional definition of what is and what is not classified as an interventional study?
- What is an intervention?
- Does administering a PRO make an (otherwise) observational study interventional?





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Is there a European definition of what is an interventional study?



**REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 April 2014**

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Nothing very clear

Article 2

(3) 'Low-**intervention** clinical trial' means a clinical trial which fulfils all of the following conditions:

- (a) the investigational medicinal products, excluding placebos, are authorised;
- (b) ...
- and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice ...

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Is there an European definition of what is not an interventional study?



REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 April 2014
on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Article 1

Scope

This Regulation applies to all clinical trials conducted in the Union.

It does not apply to non-interventional studies.

Article 2

Definitions

(4) 'Non-interventional study' means a clinical study other than a clinical trial;

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Is there an European definition of what is not an interventional study?



DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 4 April 2001
on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

(c) 'non-interventional trial':

- a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation.
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.
- **No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;**

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1.10. Question: What can be considered a “non-interventional trial”?

33. **Answer:** According to Article 1(1), 2nd period of Directive 2001/20/EC, non-interventional clinical trials are excluded from the scope of this Directive

36. The purpose for excluding these trials from the scope of the Directive 2001/20/EC is that these trials are **typically of a lower risk than interventional** clinical trials. Moreover, this restriction shall ensure that medical activities which are **normal clinical practice** and as such part of the general medical surveillance of a patient are excluded from the scope of the Directive 2001/20/EC.



Guideline on good pharmacovigilance practices (GVP)



Annex I - Definitions (Rev 3) 15 April 2014

Non-interventional studies are defined by the methodological approach used and not by the scientific objectives.

Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort and other study designs making secondary use of data).

Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. **In these studies, interviews, questionnaires and blood samples may be performed as normal clinical practice.**



VOLUME 9A - of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use – (2008)

7 - Company-Sponsored Post-Authorisation Safety Studies (PASS)

In this context it is considered important to clarify that **interviews, questionnaires** and blood samples may be **considered as normal clinical practice**. Based on these definitions a fundamental distinction can be made between non-interventional (observational) and interventional post-authorisation safety studies. The latter are considered clinical trials falling under the scope of the Directive 2001/20/EC.

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ENCEPP considerations on the definition of non-interventional trials



Agreed by ENCePP 22 November 2011

The following are general principles for procedures to still be seen as non-interventional:

- The use of **validated patient reported outcomes** is non-interventional, where evidence based medicine criteria and/or other relevant **guidelines recommend** their use for diagnostic or monitoring purposes or to measure outcomes.
- Interviews and questionnaires should not lead to a **change in behaviour** or influence treatment and should be as **short as needed** to reach the objectives of the non interventional trial.

⇒ Too many restrictive pre-requisites and difficult to check, not sure that many studies can apply to these principles...



So what is an intervention ?



Definition derived from Directive 2001/20

- Intervention related to what is added by the research protocol, and not related to usual care
- It changes the management of patients
- **In practice, a research procedure may be qualified interventional whatever the risk associated : major or minor (randomization, noninvasive examinations, questionnaires?)**
- The current definition of intervention is not in adequacy with the risk-based approach accepted by all agencies in all recent regulations (FDA, EMA)

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Europe : Comparison of national requirements



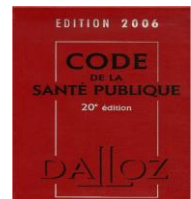
	Ethic Committee	Competent Authority	Sponsor	Insurance	Adverse event
	AT DK FR DE HU IE IT ES SE UK	AT DK FR DE HU IE IT ES SE UK	AT DK FR DE HU IE IT ES SE UK	AT DK FR DE HU IE IT ES SE UK	AT DK FR DE HU IE IT ES SE UK
	ETHICS COMMITTEE	COMPETENT AUTHORITY	SPONSOR	INSURANCE	AER
1 - CT on MP					
phase 1	█	█	█	█	█
phase 2	█	█	█	█	█
phase 3	█	█	█	█	█
phase 4	█	█	█	█	█
biotherapy	█	█	█	█	█
tissue eng	█	█	█	█	█
cell therapy	█	█	█	█	█
gene therapy	█	█	█	█	█
blood-derived	█	█	█	█	█
MAB, prot, pept	█	█	█	█	█
oligonucleotides	█	█	█	█	█
vaccines	█	█	█	█	█
fixed combination	█	█	█	█	█
multimodal	█	█	█	█	█
2 - CT on MDevice alone					
authorised	█	█	█	█	█
non authorised	█	█	█	█	█
with MP					
authorised	█	█	█	█	█
non authorised	█	█	█	█	█
3 - Other TTT trials					
radiotherapy	█	█	█	█	█
surgery	█	█	█	█	█
transplantation	█	█	█	█	█
transfusion	█	█	█	█	█
physical therapy	█	█	█	█	█
psychotherapy	█	█	█	█	█
4 - Diagnostic studies					
in vivo	█	█	█	█	█
in vitro	█	█	█	█	█
imaging	█	█	█	█	█
5 - Nutrition					
nutritional	█	█	█	█	█
nutr. Supplements	█	█	█	█	█
6 - Other clin. research					
CAR	█	█	█	█	█
biobanks	█	█	█	█	█
physiology	█	█	█	█	█
pathophysiology	█	█	█	█	█
psychology	█	█	█	█	█
7 - Epidemiology					
pharmacoepidemiology	█	█	█	█	█
interventional	█	█	█	█	█
non interventional	█	█	█	█	█
epidemiology	█	█	█	█	█
interventional	█	█	█	█	█
non interventional	█	█	█	█	█
registries of patients	█	█	█	█	█

Current French definition of non-interventional studies (Articles L. 1121-1 & R1121-2 CSP)



If the law is strictly applied, observational studies simply do not exist:
“Without any additional or unusual procedure of diagnostic or monitoring”

- All observational studies contain PRO, ClinRO... (which may not be considered currently as usual monitoring procedures)
- **Then all types of research below are interventional:**
 - PASS/PAES
 - All non-validated questionnaires: what does that mean? The SF-36 given in a new population may be considered as non validated
 - Qualitative research: interviews, cognitive debriefing, MMR
 - Every single self-questionnaire (socio-demographic, medical)
 - Online studies & patients' websites cohorts (e.g. PatientsLikeMe)



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PASS : post-authorization safety study; PAES : post-authorization efficacy study

Future French law Jardé - Waiting for a decree (LOI n° 2012-300 du 5 mars 2012)



- Risk-based approach (requirements & complexity)
 1. Non drug interventional trial at some risk
 2. **Minimal risk (non-drug) interventional trial**
 3. **Non-interventional studies** (drug & non drugs)
- Current debate whether PROs and when should apply to one of the 3 study categories, based on ?
 - Burden for subjects : number of questionnaires, items, assessments
 - Intrusiveness of items
 - Risk of destabilization ? (psychiatry)
- **Which authority will validate the study category: the heterogenous Ethics Committees ?**

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Future French law Jardé - Waiting for a decree (LOI n° 2012-300 du 5 mars 2012)



Draft list of minimal risk interventions:

- Individual or cluster randomisation
- Blood sample for research purposes
- Biological samples for research purposes
- Physiological and imaging data for research purposes
- **Interviews, audio, video or electronic ?**
- Rehabilitation exercises (physiotherapy, occupational therapy, orthophony, orthopsy)
- Visits added by the research protocol
- Psychotherapy techniques
- **Questionnaires when changing the usual care of the subject?**

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A number of voices supposedly guardians of patients' rights claim arbitrarily that questionnaires (PRO) carry a risk of destabilization and should be considered systematically as an intervention



- Irrational fear, within the area of phantasmagoria
- As soon as, as we standardize some questions about symptoms or impact of symptoms on daily life (instead of "how are you" of the doctor) into a questionnaire: it necessarily becomes an intervention
- Today protocols of qualitative research, of validation of questionnaires or epidemiological studies are rigorous and participating subjects are supervised.
- **What would add the much more complicated requirements of interventional studies ?**
- **What is the added risk ? What means destabilization ?**
- **Does it exist ? Has it been reported ?**
- **When questionnaires are aggressive, intrusive ?**

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Evaluating Iatrogenic Risk of Youth Suicide Screening Programs

A Randomized Controlled Trial



JAMA The Journal of the American Medical Association

Evaluating Iatrogenic Risk of Youth Suicide Screening Programs

A Randomized Controlled Trial

Madelyn S. Gould, PhD, MPH
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 Marjorie Kleinman, MS
 John Graham Thomas, BS
 Katherine Moskoff, CSW
 Jean Cote, CSW
 Mark Davies, MPH

Context Universal screening for mental health problems and suicide risk is at the forefront of the national agenda for youth suicide prevention, yet no study has directly addressed the potential harm of suicide screening.

Objective To examine whether asking about suicidal ideation or behavior during a screening program creates distress or increases suicidal ideation among high school students generally or among high-risk students reporting depressive symptoms, substance use problems, or suicide attempts.

Design, Setting, and Participants A randomized controlled study conducted within the context of a 2-day screening strategy. Participants were 2342 students in 6 high schools in New York State in 2002-2004. Classes were randomized to an experimental group (n=1172), which received the first survey with suicide questions, or to a control group (n=1170), which did not receive suicide questions.

Main Outcome Measures Distress measured at the end of the first survey and at the beginning of the second survey 2 days after the first measured on the profile of Mood States adolescent version (POMS-A) instrument. Suicidal ideation assessed in the second survey.

Results Experimental and control groups did not differ on distress levels immediately after the first survey (mean [SD] POMS-A score, 5.5 [9.7] in the experimental group and 5.1 [10.0] in the control group; $P=.66$) or 2 days later (mean [SD] POMS-A score, 4.3 [9.0] in the experimental group and 3.9 [9.4] in the control group; $P=.41$), nor did rates of depressive feelings differ (13.3% and 11.0%, respectively; $P=.19$). Students exposed to suicide questions were no more likely to report suicidal ideation after the survey than unexposed students (4.7% and 3.9%, respectively; $P=.49$). High-risk students (defined as those with depression symptoms, substance use problems, or any previous suicide attempt) in the experimental group were neither more suicidal nor distressed than high-risk youth in the control group; on the contrary, depressed students and previous suicide attempters in the experimental group appeared less distressed ($P=.01$) and suicidal ($P=.02$), respectively, than high-risk control students.

Conclusions No evidence of iatrogenic effects of suicide screening emerged. Screening in high schools is a safe component of youth suicide prevention efforts.
 JAMA. 2005;293:1628-1642 www.jama.com

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©2005 American Medical Association. All rights reserved. Reprinted JAMA, April 6, 2005—Vol 293, No 13 1635

Conclusions

No evidence of iatrogenic effects of suicide screening emerged. Screening in high schools is a safe component of youth suicide prevention efforts.



There are thousands of web quiz more or less validated on all sorts of health issues and without supervision



If qualitative research, validation of questionnaires and epidemiological studies have a risk of destabilization, then these numerous websites should be banned

Psychology Today

Home Find a Therapist Topic Streams Get Help Magazine Tests

Depression Test
101 questions, 20 min.

PROGRESS STATUS:

	Most of the time	Often	Sometimes	Rarely	Almost never
	1	2	3	4	5
1. I feel sad.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. I feel agitated or restless (I pace, am unable to stay calm, or need to move constantly).	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. I feel worn out.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. I feel so guilty that I can barely take it.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. When I wake up in the morning, I feel like there is nothing to look forward to.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. I think about death.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. When needed, I can make up my mind quickly.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. I get mad at myself if I do not achieve the goals I have set out to reach.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. When something is bothering me, I cannot stop thinking about it.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Next

Illness Quiz

Home OCD Test PTSD Test Depression test Anxiety Test

You are 100% suicidal.

Are You Suicidal

This test will try to measure your depression level and will check your coping ability. Please answer below questions honestly and you will find whether you are suicidal or not.

You are 100% suicidal.

You are suicidal: 100%

Level: Very High

You should Discuss your result with our [psychic here](#) (Free)

You Have Signs Of Bipolar Disorder So Please Take [Bipolar Test Here](#).

Where is the real risk of destabilization ?

Validation or use of a questionnaire in a supervised research setting ?

The Aggression Scale:

Please answer the following questions thinking of what you actually did during the last 7 days. For each question, mark with a circle how many times you did that behavior during the last 7 days.

During the last 7 days	0 times	1 time	2 times	3 times	4 times	5 times	6 or more times
1. I teased students to make them angry.	0	1	2	3	4	5	6+
2. I got angry very easily with someone.	0	1	2	3	4	5	6+
3. I fought back when someone hit me first.	0	1	2	3	4	5	6+
4. I said things about other kids to make other students laugh.	0	1	2	3	4	5	6+
5. I encouraged other students to fight.	0	1	2	3	4	5	6+
6. I pushed or shoved other students.	0	1	2	3	4	5	6+
7. I was angry most of the day.	0	1	2	3	4	5	6+
8. I got into a physical fight because I was angry.	0	1	2	3	4	5	6+
9. I slapped or kicked someone.	0	1	2	3	4	5	6+
10. I called other students bad names.	0	1	2	3	4	5	6+
11. I threatened to hurt or to hit someone.	0	1	2	3	4	5	6+

Abuse of daily aggressive TV news & films and video games ?

By MICHAEL CASEY | CBS NEWS | August 17, 2015, 2:00 PM

Do violent video games lead to criminal behavior?



“The research demonstrates a consistent relation between violent video game use and increases in aggressive behaviour, cognitions and affect, and decreases in pro-social behaviour, empathy and sensitivity to aggression.”
APA Task Force on Violent Media (2015)

European Perspective - Conclusion



- No clear definition of what is a non-intervention
- No clear statement of the place of PROs (interviews, questionnaires)
- Heterogeneous requirements among the 28 Countries
- Heterogeneous appraisal by Ethics Committees
- **Need for an harmonized European regulation on non-interventional studies (and on PRO which are an essential part of these studies) but with requirements adapted to the risk-based approach**

PROs : interviews, questionnaires, epidemiological studies

- In fact: no intervention of staff or physician
- More an interaction between a subject and a paper/tablet
- **No evidence of any harm or destabilization reported**
- **Should be considered as a non-intervention by default**

Regulation – the real threat to clinical research. BMJ 2008



Stewart P, et al



Jean Paty, PhD

Principal, Advisory Services
Quintiles, USA



Erin Tomaszewski

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Is there a US definition of what is an interventional study?



- The frequently applied criteria for a defining a study as interventional in the US are:
 - Intervention is assigned according to a protocol
 - Assessment of health outcomes according to the protocol
- WHO glossary¹
 - “... any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials...”
- Clinicaltrials.gov²
 - “...participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior...”

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1. <http://www.who.int/ictrp/glossary/en/>
2. <https://www.clinicaltrials.gov/ct2/about-studies/learn#ClinicalTrials>

Is there a US definition of what is not an interventional study?



- In the US, there is no clear guidance from the FDA, nor consistent definition of what constitutes observational research
- The most frequently applied criteria for a defining a study as observational are:
 - Intervention is part of routine care, no assignment of the intervention
 - Assessment of health outcomes according to the study protocol
- Clinicaltrials.gov
 - “...investigators assess health outcomes in groups of participants according to a research plan or protocol
 - Participants may receive interventions (which can include medical products such as drugs or devices) or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator...”

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So what is an intervention ?



- Intervention is defined in the research protocol and changes the way a patient is treated
- These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, such as diet

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Institutional Review Board



- IRBs tend to accept studies as observational even when there are several PROs administered
- In rare circumstances, IRBs may deem that the mere collection of patient reported data via PROs in a registry is enough ‘interference’ with the natural follow up to tip the scales towards classifying a registry or observational study as an interventional study
- HHS IRB Expedited Review Process for ‘minimal risk’ studies are those that have:
 - “...Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110...”

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HHS.gov
U.S. Department of Health & Human Services

Does administering a PRO make a study interventional?

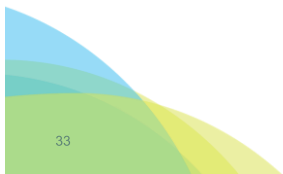


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US Perspective - Conclusion



- There are no clear guidance on observational studies in the US
- Administering PROs in observational studies in the US is not considered a protocol driven intervention
 - At times, the IRB may consider PROs to be interventional, this is on a case by case basis
- Administering PROs is not an intervention, it is a way to collect data on the reality of living with a disease

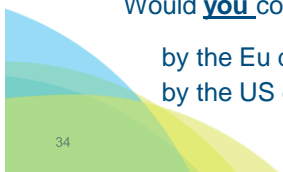


Hypothetical example 1

- Prospective Phase 4 “observational” study to assess long-term (36 month) safety and efficacy with drug X in the treatment of adult epilepsy
 - Non-randomized 2-cohort study (drug X, SoC); tx decided prior to enrolment
 - Primary endpoint: seizure frequency & severity (VA Seizure Frequency & Rating Scale)
 - Secondary endpoint: suicidal ideation and behaviour (eCSSRS)
 - Secondary endpoint: health status (SF-36, EQ-5D)
 - Secondary endpoint: quality of life (QOLIE)
 - Exploratory endpoint: Healthcare resource utilization

Would you consider this as interventional?

- by the Eu definitions?
- by the US definitions?



Hypothetical example 2

- Prospective Phase 4 “observational” study to assess medium-term (12 month) safety and efficacy with drug Y in the treatment of psoriasis in adolescents (12-18 years)
 - Non-randomized 1-cohort study
 - Primary endpoint: psoriasis severity (PASI)
 - Secondary endpoint: itch (NRS completed as a 7-day diary once per month)
 - Secondary endpoint: quality of life (PQOL)

Would you consider this as interventional?

by the Eu definitions?
by the US definitions?

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Hypothetical example 3

- Prospective Phase 4 “observational” study to assess short-term (3 month) efficacy of drug Z in the treatment of paediatric type 1 diabetes (0-6 years)
 - Non-randomized 3-cohort study (drug Z, drug A, “other”); tx decided prior to enrolment
 - Primary endpoint: HbA1c
 - Secondary endpoint: Caregiver burden (new scale)

Would you consider this as interventional?

by the Eu definitions?
by the US definitions?

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Questions and comments



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Conclusion

- PATIENT-REPORTED OUTCOMES: CAN THEIR USE IN OBSERVATIONAL (“REAL-WORLD”) RESEARCH BE CONSIDERED INTERVENTIONAL?
 - Yes – considerations relate to amount and deviation from routine care
 - Complexities of cross-country research
- PATIENT-REPORTED OUTCOMES: **SHOULD** THEIR USE IN OBSERVATIONAL (“REAL-WORLD”) RESEARCH BE CONSIDERED INTERVENTIONAL?
 - No in clinical research.....except in very few cases
 - “minimally interventional” may be an appropriate label in this case!
 - Sometimes in clinical practice!

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