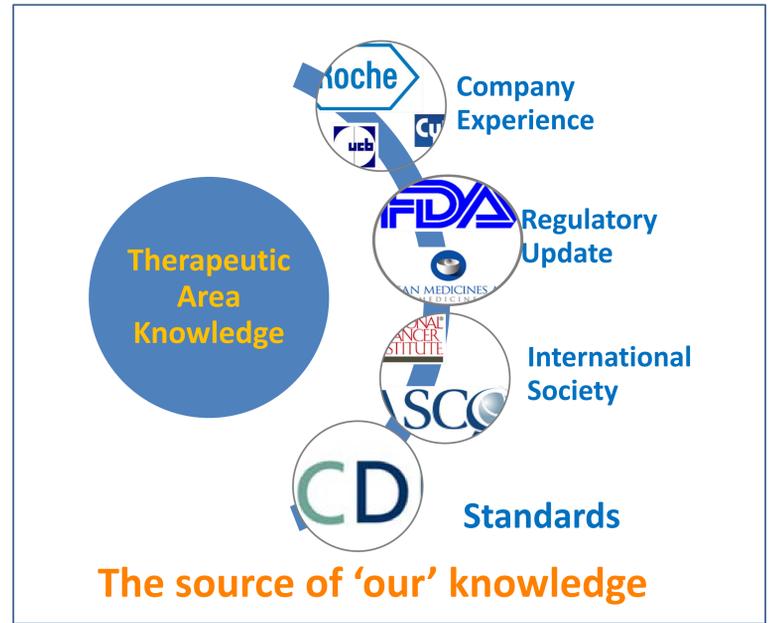


ABSTRACT

While the evolution of information technology is improving data accessibility for customers for their own exploration, the need for comprehensive understanding of therapeutic area knowledge for programmers in clinical development is increasing. A basic understanding of the medical background and any special assessment methods or ways of statistically analyzing and displaying the data would improve interactions between programmers and partners e.g. scientists, statisticians etc.

In this intent, activities to collect and provide comprehensive information around the Oncology, Parkinson's disease and Rheumatoid Arthritis Therapeutic Areas (TA) via the PhUSE Wiki had started in the last years. Various PhUSE members have spent time and energy in providing and expanding their knowledge and making it available to the entire community.

Since the last annual PhUSE conference, these TA pages were further updated and, in addition, information regarding epilepsy has recently been added to the PhUSE Wiki. Although there remains much to do in order to complete and maintain the collected material, Wikis are deemed a useful tool for Statistical Programmers approaching these TA for the first time or for those who wish to improve their knowledge. Moreover the PhUSE Wiki can be seen as a basic tool for future developments to improve the way professionals in the different TA work. An established working relationship across organizations, pharmaceutical companies or external service providers, will help to support implementation of TA-specific standards from mapping raw data in SDTM, data analysis using ADaM and finally data presentation in standardized outputs. The PhUSE Wiki can be the central place to share important updates such as new CDISC TA standards or the availability of new TA regulatory guidance. On the other hand we see the Wiki as a place to discuss, to stimulate and inspire new initiatives among the "SAS-Programming Community". This may include specific TA working related white papers and/or scripts being part of the FDA Working Groups WG5 "Development of Standard Scripts for Analysis and Programming" Project 08 "Create white papers providing recommended display and analysis including Table, List and Figure shells".



PATIENT CENTRICITY

- Main theme of PhUSE 2013
- What does patient centricity mean for Statisticians and Statistical Programmers?
- Understanding the Therapeutic Areas you work on:
 - Regulatory Environment
 - Endpoints
 - Study Designs
 - Data Collection/Challenges
 - Use of Standards e.g. CDISC

→ An attempt to answer

THE THERAPEUTIC AREA PHUSE WIKI PAGE

- What is Wiki*
 - A tool to support collaboration
- What is PhUSE Wiki
 - A PhUSE/FDA/Industry Wiki tool to share information specifically relating to clinical trial information
- What is PhUSE TA Wiki
 - A tool to share TA-specific knowledge and to help improve the way professionals work
 - Central place to share
 - regulatory framework
 - implementation of standards
 - TA-specific information from all over the internet
- Who can benefit from PhUSE TA Wiki
 - Starting point for Beginners in TA
 - Professionals benefit from lessons-learned in real-life and can share their own experience

Use case: Epilepsy

Contents [hide]

- Introduction
- Disease Description
 - 1.1 Etiology
 - 1.2 Seizure types
- Agency Guidelines
 - 3.1 FDA
 - 3.2 EMA
 - 3.3 Japan (Ministry of Health and Welfare)
- Clinical Trial Endpoints
 - 4.1 Efficacy assessment
 - 4.2 Safety assessment
- Clinical Trial Design
- Data Challenges
- Data collection
- SDTM
- ADaM
- Statistical Analysis
- References
- Project Team

Seizure types

Following epileptic seizures classification is based on ILAE proposal of 2010:

Partial seizures	Generalized seizures	Unknown
Simple partial seizure	Absence	Unknown
Complex partial seizure	Myoclonic	
	Clastic	
	Tonic	
	Tonic-clonic	
	Abscic	

Partial (focal, local) seizures

Partial (focal) seizures occur when this electrical activity remains in a limited area. The differentiation between simple and complex partial seizures is a matter of degree. The differentiation between simple and complex partial seizures is a matter of degree. The differentiation between simple and complex partial seizures is a matter of degree.

General Background

The FDA guideline [7] [8] has remained the same for more than 30 (1) years. The last changes were made in 1981. The guideline discusses clinical trial setups for phase I/III studies in both adults and children. It is a relatively small document (10 pages of main text) and mainly addresses long-term therapy of seizure disorders. However, clinical endpoints are mentioned in the guideline although no further advice, e.g. about non-inferiority/superiority margins is given. Measurements of efficacy include reduced seizure frequency and increased seizure-free intervals. Apart from seizure diaries, patient reported outcomes (PRO) are not discussed which may also be due to the relative age of the guideline. All in all the FDA guideline leaves much room for interpretation on how a trial should be designed to be sufficient for submission to the FDA.

EMA

The EMA Guideline [8] [9] is currently available as second revision and was issued in 2010. This relatively new guideline gives a general overview on prevalence and aetiology of the disease as well as current (as of 2010) success of therapy with Anti-epileptic Drugs (AED). The main text gives detailed instructions on selection of the study population under investigation. Populations are selected according to epileptic syndrome, seizure type and age of study subjects. The development of drugs in children and in the elderly is discussed in two separate sections to address special considerations in these patient cohorts. The assessment of efficacy is discussed in detail for a variety of study designs with explicit statements on duration of studies, (primary) efficacy parameters and PRO instruments. General considerations on the statistical analysis of efficacy are also provided. As opposed to the FDA guideline the primary efficacy endpoint is defined as analysis of responders/non-responders, where responders are patients who obtained at least a certain pre-defined percentage reduction of seizure frequency. Therefore in studies submitted to both FDA and EMA both endpoints are defined, where reduction in seizure frequency is used in the US and percentage of seizure reduction is used in Europe (see Clinical Trial endpoints for details). There are clear statements on the methodology of studies in the development of a new anti-epileptic drug for both Add-on and Monotherapy.

Japan (Ministry of Health and Welfare)

Trial Design and Trial Endpoints

Clinical Trial Design

Study designs usually start with a baseline period during which the subject does not receive any study drug. This period is mainly to assess baseline seizure counts. The baseline period needs to have a certain length to be able to detect a reasonable amount of seizures as well as changes in seizure frequencies. This phase is also needed to finally confirm that subjects are eligible, e.g. number of seizures fits the study design, concomitant AED(s) are stable etc.

Clinical Trial Endpoints

Efficacy assessment

- Change in seizure frequency
- Seizure-free intervals
- Responder analysis (i.e. subjects achieving 50% reduction in seizure frequency)
- Decreased total seizure time
- Improved functional capacity
- Decreased incidence of adverse reactions
- Decreased generalization of focal seizures
- Quality of Life (e.g. QOLIE-31-P)

The assessment of efficacy is primarily based upon seizure frequency and occurrence. This is due to the primary goal of treatment in epilepsy: seizure freedom of subjects.

Safety assessment

- Extend of exposure
- Evaluation of treatment-emergent adverse events (TEAE)
- Evaluation of TEAE of interest

The overall safety assessment does not differ much from evaluations done in other therapeutic areas. However, there is a special focus on TEAE of interest

Data Challenges and Statistical Analysis

outstanding!
What are your experiences?

We're Looking for Contributors/Reviewers

Use case: Oncology

Contents [hide]

- Introduction
- Disease Description
 - 2.1 Cancer Statistics
 - 2.2 Causes and Risk Factors
 - 2.3 Treatment
- Agency Guidelines
 - 3.1 FDA
 - 3.2 EMA
 - 3.3 Japan (Ministry of Health and Welfare)
- Clinical Trial Endpoints
 - 4.1 Overall Survival
 - 4.2 Progression Free Survival
 - 4.3 Time to Event
- Clinical Trial Design
- Data Challenges
- Data collection
- SDTM
- ADaM
- Statistical Analysis
- References
- Project Team

Introduction

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems.

Disease Description

All cancers begin in cells, the body's basic unit of life. To understand cancer, it's helpful to know what happens when normal cells become cancer cells. The body is made up of many kinds of cells. These cells grow and divide in a...

Agency Guidelines

FDA

FDA Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007) The Guidance contain general regulatory requirements for efficacy

General Background

Clinical Trial Endpoints

Overall Survival (OS)

Overall survival (OS) has been the gold standard for oncology clinical trial endpoints. Over the years, however, some surrogate endpoints (i.e. as objective response rate and progression free survival (PFS)) have been employed because they are believed to be more predictive of overall survival (OS) than OS itself.

Time to Event Measurements

Best Overall Survival Response for Solid Tumors (BOS) - Defined as per RECIST criteria [10] where BOS is the best response recorded from the start of the study treatment until the end of treatment.

Progression Free Survival (PFS)

Phase I dose escalation

Phase I studies are a critical step in cancer drug development. They are small sample size and non-randomized and they also produce early observations about the drug's safety, pharmacokinetics, and preliminary evidence of efficacy.

Phase I studies

A phase I clinical trial in oncology is the first test of the new treatment (new drug or new combination of drugs) in human to safely check and assess [11] [12].

- The right amount of the drug (Dose) - (Maximum Tolerated Dose) that causes the fewest side effects.
- The safety and the Pharmacokinetics (PK) of the drug in the body.

Data Challenges and Statistical Analysis

Overview

The way data are collected and handled in Oncology studies is pretty standard, although there are some peculiarities. Usually a CRF is developed by collecting subject characteristics at study entry, such as Age (and/or date of birth), Sex, Race, Weight, Height, etc., followed by information about cancer diagnosis and prior cancer therapies when subjects are previously diagnosed with cancer.

Comparison of Survival Distributions of Time to Event Endpoints (Kaplan Meier Method)

The analysis of time to event endpoints is based on the survival function, which is the probability to survive or, more generally, to stay event-free beyond a certain point in time for an intervention to survival analysis, see Time to Event Clinical Trials [13].

Existing Standard

Potential New Standard

Key References

1. FDA Guidance on the evaluation of anticancer medicinal products in man
2. ICH E9 (R1) Addendum to the ICH E9 guideline on clinical trials on medicinal products for human use
3. ICH E10 Addendum to the ICH E10 guideline on the evaluation of anticancer medicinal products in man
4. ICH E11 Addendum to the ICH E11 guideline on the evaluation of anticancer medicinal products in man
5. ICH E12 Addendum to the ICH E12 guideline on the evaluation of anticancer medicinal products in man
6. ICH E13 Addendum to the ICH E13 guideline on the evaluation of anticancer medicinal products in man
7. ICH E14 Addendum to the ICH E14 guideline on the evaluation of anticancer medicinal products in man
8. ICH E15 Addendum to the ICH E15 guideline on the evaluation of anticancer medicinal products in man
9. ICH E16 Addendum to the ICH E16 guideline on the evaluation of anticancer medicinal products in man
10. RECIST 1.1
11. FDA Guidance on the evaluation of anticancer medicinal products in man
12. ICH E9 (R1) Addendum to the ICH E9 guideline on clinical trials on medicinal products for human use
13. ICH E10 Addendum to the ICH E10 guideline on the evaluation of anticancer medicinal products in man

* A wiki is a website which allows people to add, modify, or delete the content via a web browser usually using a simplified mark-up language or a rich text editor. Wikis use specialized wiki software and are usually created collaboratively. PhUSE 2013 What I Know is N. Guerro (PP16)

CONCLUSION

- As an initial outcome two TA workshops, Oncology and Rheumatoid Arthritis, were delivered at PhUSE 2013 in Bruxelles
- PhUSE TA Wiki is seen as a useful tool as updates are ongoing and new indications added
- Adding information related to Epilepsy in PhUSE TA Wiki page led to further insights for contributors
- An interesting collaboration possibility across pharma companies and CROs
- Seeking for feedback on Structure, Sections, Topics covered
- Maintenance can be problematic

Everyone is invited to contribute! <http://www.phusewiki.org> For further information: wikiadmin@phusewiki.org