Randomized Clinical Trial
(RCT)
Good Clinical Practice
(GCP)

Mansour Shamsipour

Epidemiologist

Clinical Trial Center

Tehran University of Medical Sciences

shamsipour@sina.tums.ac.ir

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Objectives

- Overview of Epidemiological Study Designs
- Central role of **causal inference**
- Introduction to Clinical Trials
- Key **characteristics**
- Drug Development Process
- Importance of **evaluating safety and efficacy**
- Different stakeholders
- Clinical trial **ecosystem** and **responsibilities**

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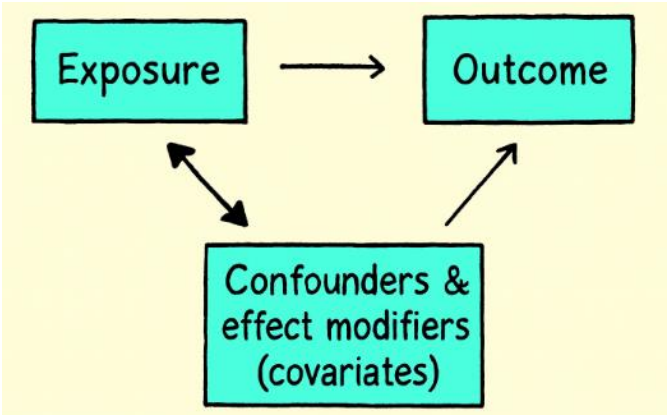
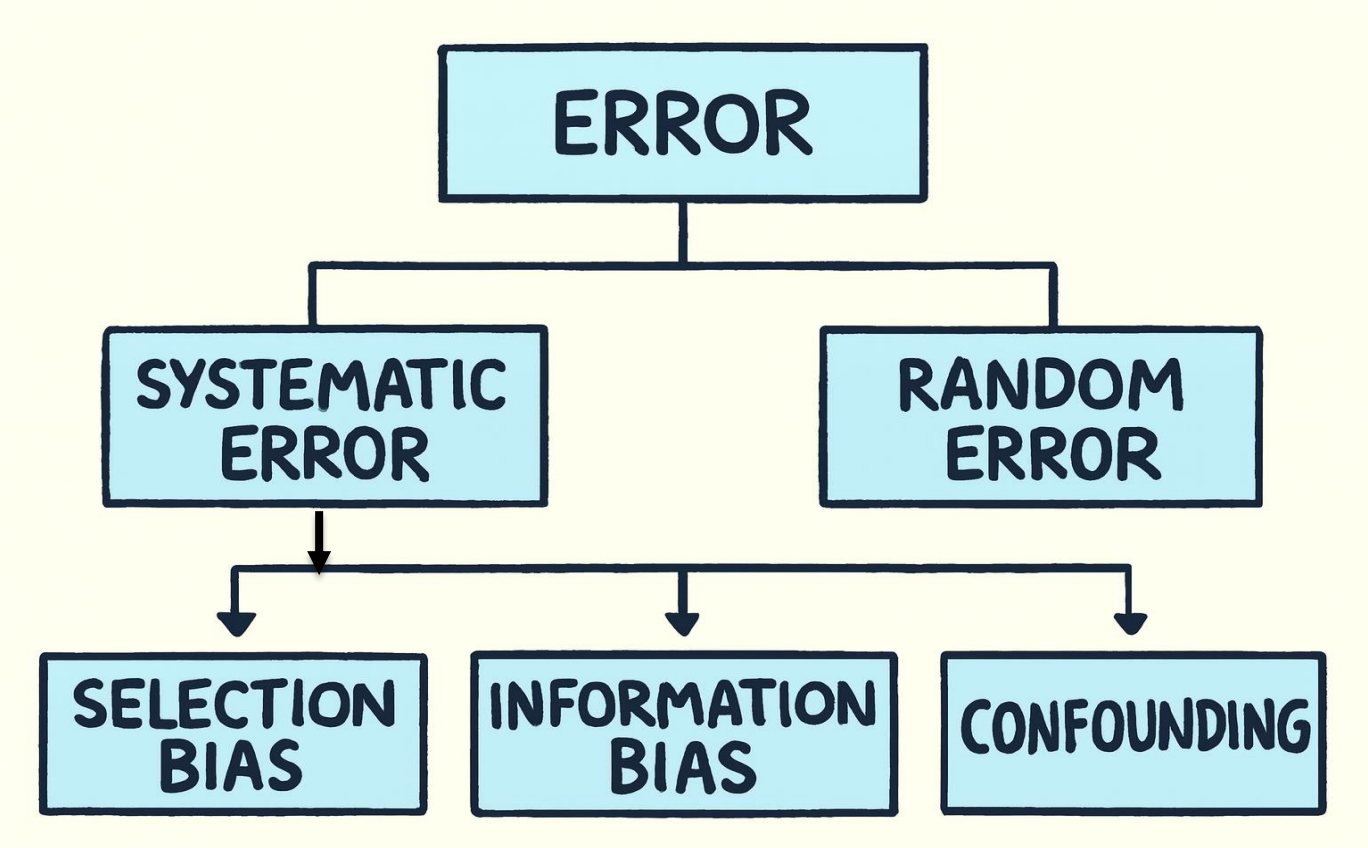
Epidemiological Study

- A major goal of epi research is:
- To explain patterns of disease occurrence
- and
- Causation (etiology)



Random and Systematic Error



The best epidemiologic study will be one that captures the causal effect of interest with minimal distortion (error)

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Importance of Study Design

Foundation of Valid Research:

- Determines how data is : Collected, analyzed, and interpreted.
- **Minimizes Bias & Confounding**:
- Strong designs (e.g., RCTs, cohort studies) reduce systematic errors.
- **Ensures Ethical & Efficient Use of Resources**:
- Prevents wasted time, funding, and participant burden.
- **Impacts Causality vs. Association:**
- **Bottom Line**: The **right study design** turns a good research question into **trustworthy**, actionable evidence.

Evidence-Based Medicine

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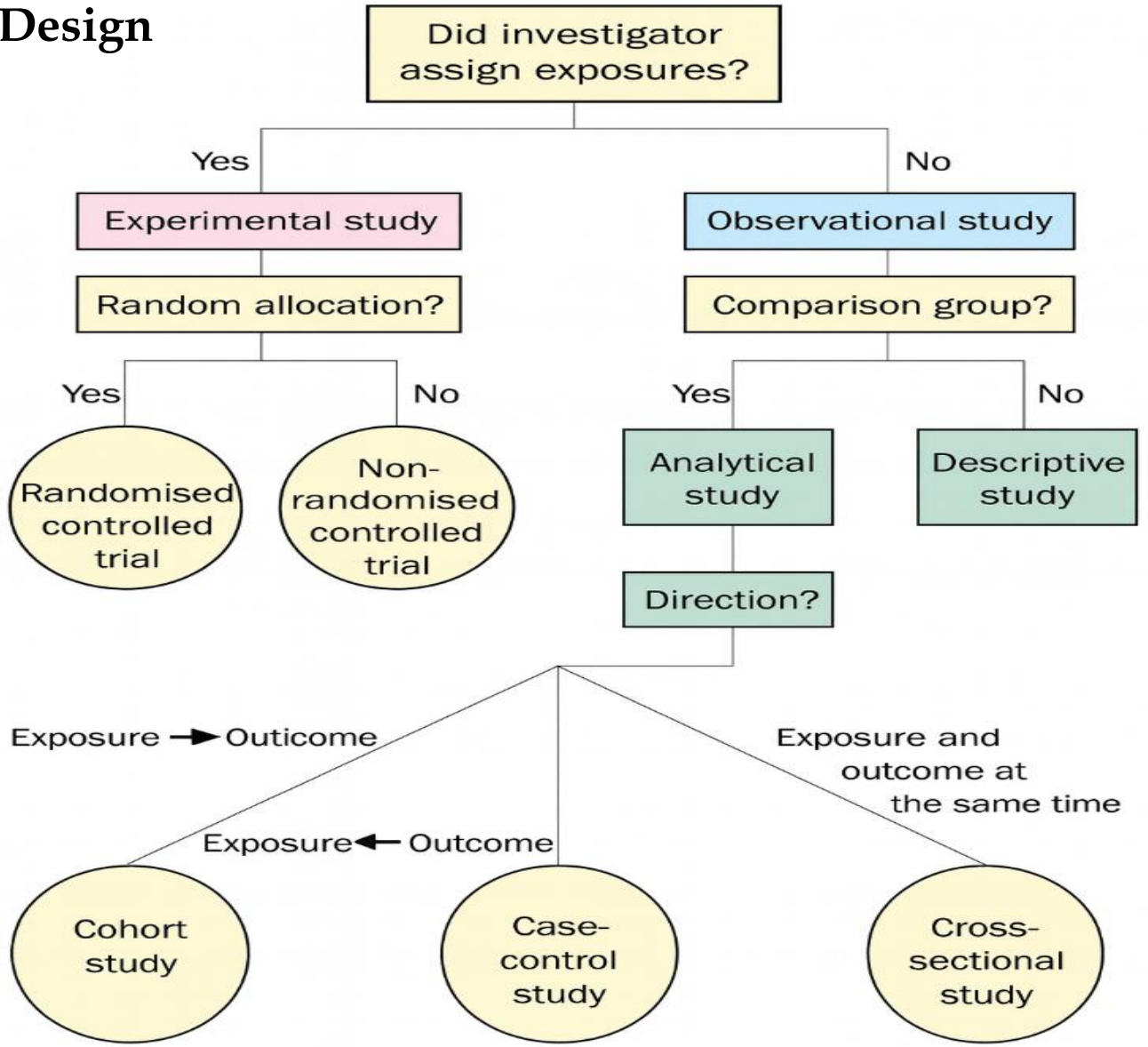
Study Design



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Introduction to Clinical Trials

Definition of a Clinical Trial

- A clinical trial is a prospective, controlled, experimental study conducted in human participants to evaluate the safety, efficacy of one or more medical interventions—such as drugs, devices, surgical procedures, behavioral therapies, or preventive strategies—by comparing outcomes between assigned groups under standardized conditions.

- **Key Characteristics** : Prospective, Control group, Active intervention assignment, Human, Safety, Efficacy , Pre-specified Outcomes.

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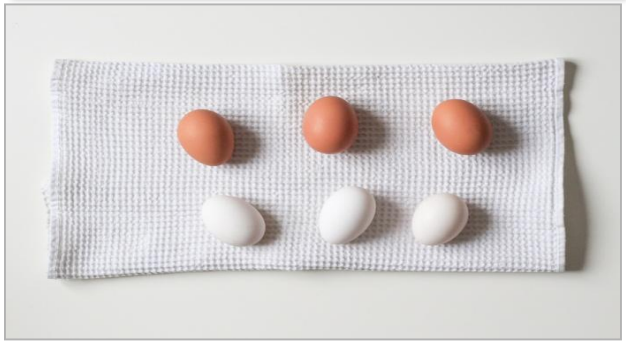
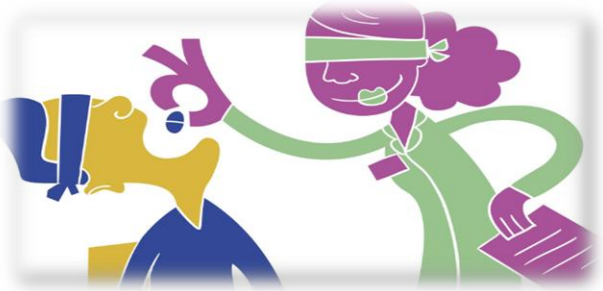
Core Prerequisites

- **Eligibility Criteria**
- Ensures a comparable, homogeneous population.
- Red line: Enrolling ineligible participants selection bias.

- **Randomization**
- Balances known/unknown confounders.
- Red line: Improper or predictable allocation invalidates causality.



- **Blinding**
- Prevents performance & detection bias.
- Red line: Unblinding → distorts outcomes & interpretation.



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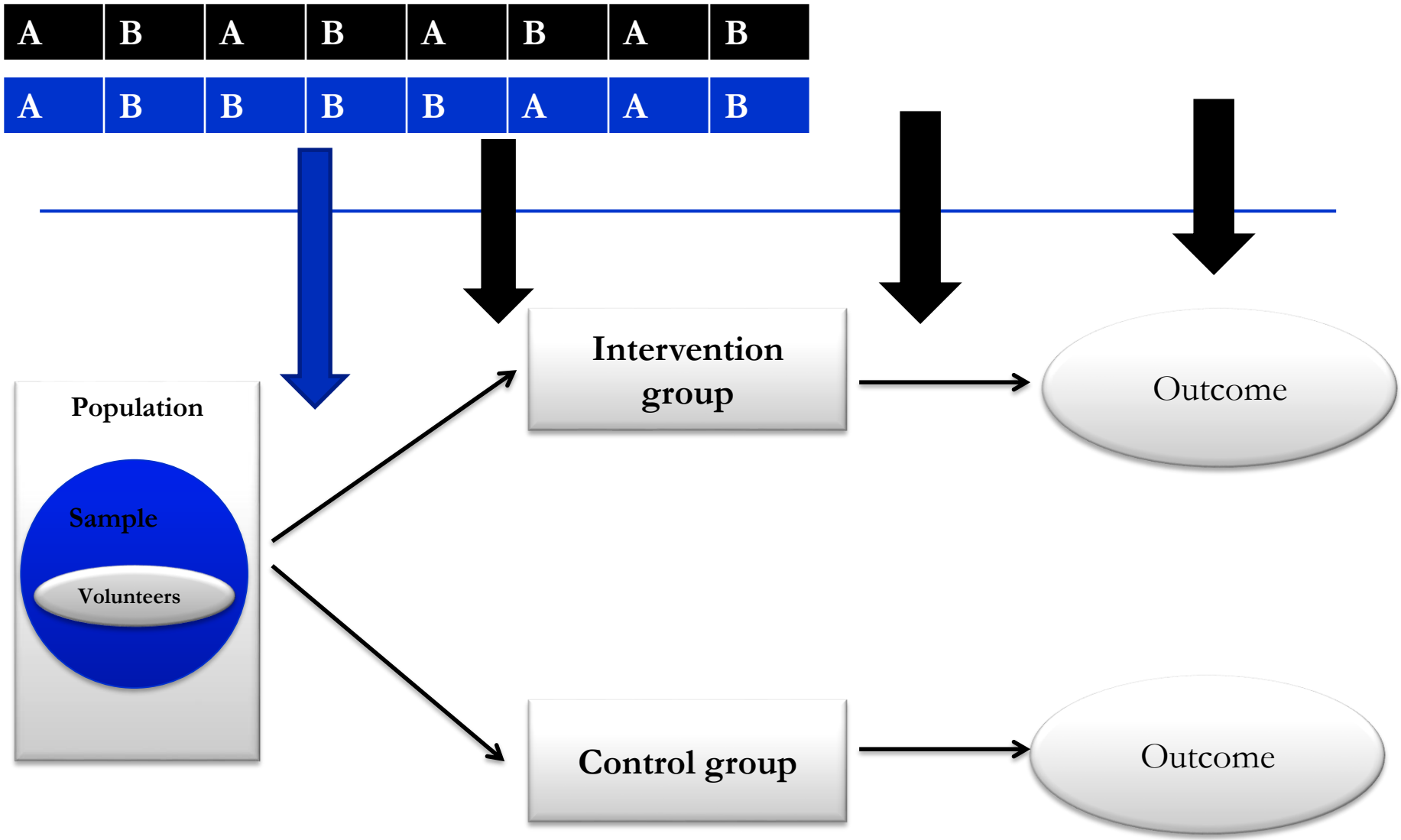
The Solution: RCTs

- Random assignment creates comparable groups.
- Difference in outcomes between groups
- ≈ Average Treatment Effect
- ATE = Mean(outcome | treated) – Mean(outcome | control)
- RCTs provide the best available estimate of the counterfactual



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Drug Development Process

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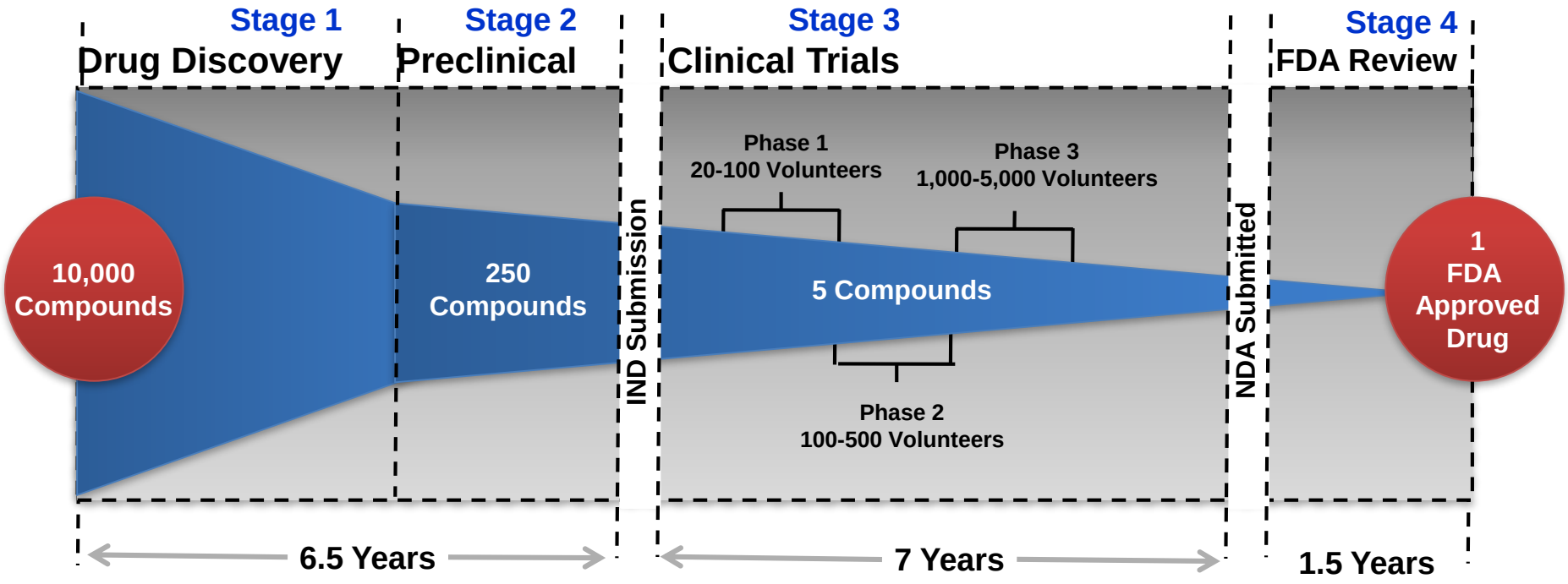
A Slow and Costly Process



Source: Pharmaceutical Research and Manufacturers of America

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Good Clinical Practice
GCP

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What is GXP?

- GXP stands for Good X Practice
- Set of guidelines and standards ensuring quality, safety, and efficacy
- GMP - Good Manufacturing Practice
- Ensures quality in manufacturing processes
- Prevents contamination and errors
- GLP - Good Laboratory Practice
- Standards for laboratory testing
- Ensures accuracy and reliability of data
- GCP - Good Clinical Practice

Good Clinical(Research) Practice (GCP) principles

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Brief History of GCP

- 1947 - **Nuremberg Trials**: Nuremberg Code established ethical guidelines for human research.
- 1964 - **Declaration of Helsinki**: Ethical standards introduced by the World Medical Association.
- 1960s - **Thalidomide Tragedy**: Birth defects led to stricter clinical trial regulations globally.
- 1996 - ICH GCP Guidelines: ICH formalized GCP, ensuring participant safety and data integrity.
- Global Adoption: FDA, EMA, and others made GCP a standard for clinical trials worldwide.(**European Medicines Agency)**

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ICH E6-R2: Good Clinical Practice: Consolidated Guideline

- Good Clinical Practice" (GCP) is an international ethical and scientific standard governing clinical trials.
- It ensures ethical trial design, conduct, monitoring, and accurate reporting.
- Compliance with GCP safeguards participants' rights, safety, and well-being while maintaining credible trial data.

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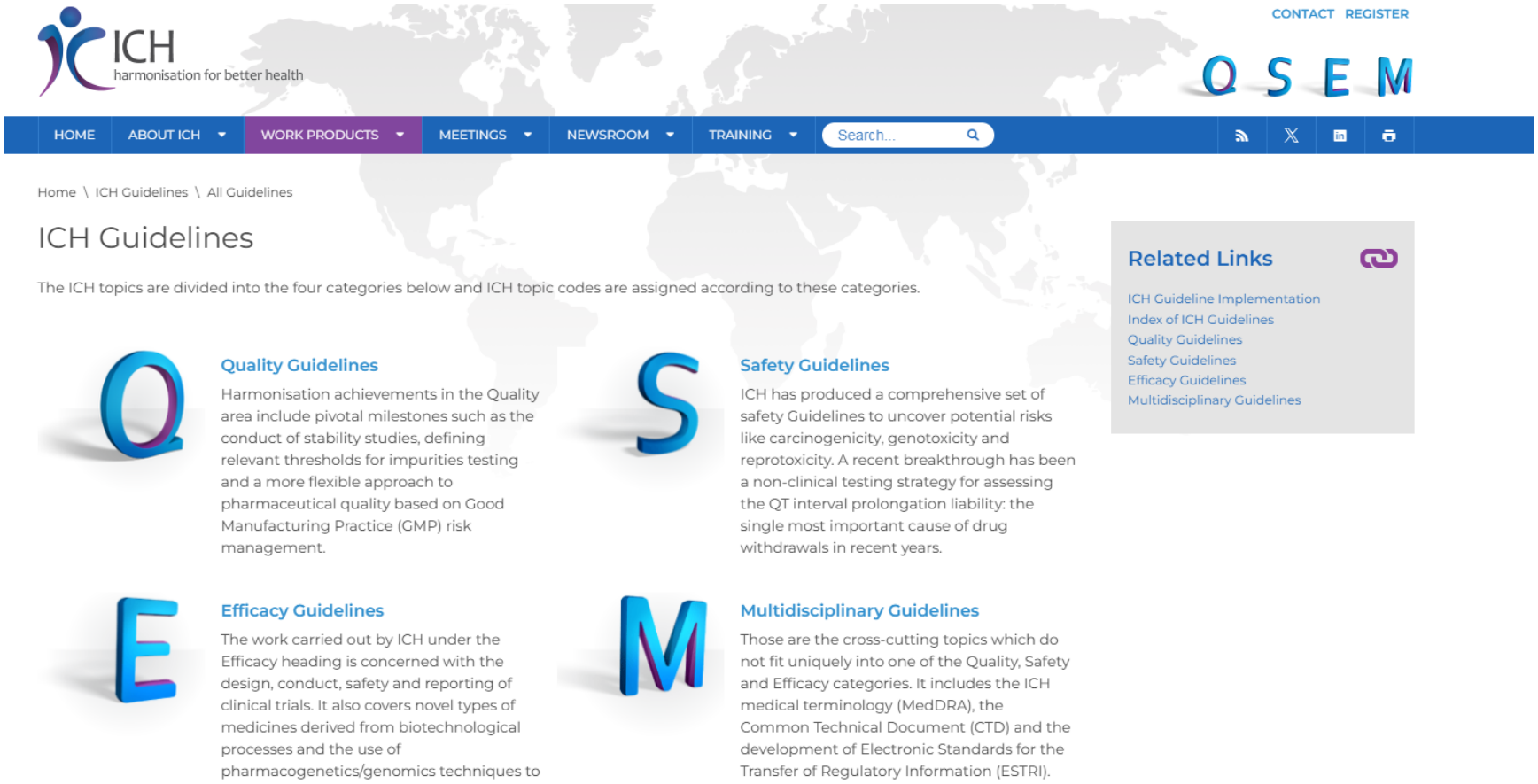
ICH



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13 Principles of GCP

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GCP principles categories

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Ethics principles

- 1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
- 2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society.
- – A trial should be initiated and continued only if the anticipated benefits justify the risks.

- 3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

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Protocol and science principles

- 4- the available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

- 5- Clinical trials be scientifically sound and described in a clear, detailed protocol

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Responsibilities principles

- 6- The IRB/IEC must approve the protocol prior to the initiation of the trial and that it be conducted as it has been approved.

- 7-Medical care given, medical decisions be made by appropriately qualified physicians/dentist.
- 8 - The investigators and their study teams: qualified by education, training, and experience to perform their respective task(s).

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Informed consent

- 9- The concept of freely given informed consent
  - Consent is voluntary,
  - All necessary information is disclosed appropriately and in a language understandable to the potential participant,
  - The potential participants are able to make an informed decision, in other words, that they are capable of rendering a independent decision.
  - The **process** of engaging with potential participants about the study and their willingness to join.

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Data quality and integrity principles

- 10 - All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification(CRF).

- 11- The privacy and confidentiality of all records that could potentially identify subjects, and calls attention to applicable regulatory requirement(s).

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Investigational product

- 12- All investigational products should be
  - Manufactured,
  - Handled,
  - and Stored
- in accordance with applicable Good Manufacturing Practices (GMP).
- All investigational products should be used in accordance with the approved protocol.

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Quality assurance and quality control (QA/QC)

- 13- Systems with procedures that assure the quality of every aspect of the trial should be implemented.

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In summary

Good Clinical Practice (GCP) puts into action 13 principles for the conduct of clinical trials that ensure

Ethics	Quality	Compliance

These principles incorporate the essential elements of GCP

Valid methodology and data quality	Balance between risks/benefits	Independent Ethical Review	Informed Consent

اصول اخلاق در کارآزمایی بالینی

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اصول محافظت از آزمودنی انسانی

- بیشتر متن هایی که به اخلاق در پژوهش پرداخته اند،
- سه اصل را بنیادهای اساسی توجه به رعایت اصول اخلاقی در پژوهش می دانند:
  - **أصل احترام به استقلال فردی**
  - **اصل خیررسانی**
  - **و اصل رعایت عدالت.**
- این سه اصل در روند پژوهش با رعایت سه موضوع:
  - **رضایت آگاهانه**
  - **ایجاد تعادل در سود و زیان پژوهش،**
  - **و نحوه انتخاب آزمودنی** آمیخته می شود.

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احترام به استقلال فردی (autonomy)

- احترام به استقلال فردی دو تعهد اخلاقی در پی دارد:
  - اول آن که افراد مستقل و مختار تلقی شوند، هیچ مانعی در راه اعمال این اختیار قرار نگیرد،
  - دوم اینکه حمایت از افرادی است که اختیار کامل ندارند.
    - ✓ بعضی افراد به سبب بیماری، عقب ماندگی ذهنی یا شرایطی خاص (مانند زندانی بودن) اختیار محدود دارند.
    - ✓ اصل احترام در مورد این افراد به معنای حمایت از آنان در برابر زیانی است که احتمال دارد به سبب محدود بودن اختیار برایشان پیش آید.

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اصل خیر رسانی (beneficence)

- کارها و کوشش هایی است که برای فرد سودمند، مطلوب و منفعت رسان باشد.
- این اصل دست کم تعهدهای صدمه نزدن به فرد و رساندن بیشترین فایده و کمترین زیان به فرد را در بر دارد
- ارزیابی توازن سود و ضرر

اصل عدالت (justice)

- چه کسی از نتیجه پژوهش سود می برد و زیان آن نصیب چه کسی می شود؟
- پژوهش درباره چه افرادی صورت می گیرد و چه کسانی از نتیجه آن استفاده می کنند؟
- توزیع عادلانه سود و زیان پژوهش در گروه های اجتماعی، جنسی و نژادی است.
- در سال ۱۹۴۰ میلادی، طرحی پژوهشی با هدف تبیین سیر طبیعی بیماری سیفیلیس انجام شد (مطالعه توسکگی که آزمودنی آن تنها افراد فقیر و بی چاره سیاه پوست روستایی بودند، درحالی که سیفیلیس تنها در این گروه شایع نبود و در طبقه های متوسط و بالای جامعه نیز وجود داشت.
- عدالت حکم می کند که زحمت ها، خطرها، سودها، و نتایج پژوهش به گروهی خاص منحصر نشود و برای استفاده گروهی ویژه نباشد.
- توزیع عادلانه زحمات و منافع پژوهش در گروه های مختلف مردم به معنای رعایت اصل عدالت در پژوهش است.

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کاربرد اصول سه گانه اخلاق در پژوهش

رضایت آگاهانه

- اجرای اصل احترام به استقلال فردی
- گرفتن رضایت نامه مهمترین گام عملی در رعایت اصول اخلاقی و محافظت از ازمودنی است
- رضایت باید آگاهانه و آزادانه باشد

- آنچه در چگونگی و ساختار رضایت آگاهانه به طور مشترک در بیشتر بیانیه ها و منابع شامل سه بخش بیان اطلاعات اساسی، قابل درک بودن اطلاعات برای آزمودنی، و داوطلب و مختار بودن آزمودنی در دادن رضایت است.
-

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رضایت آگاهانه

- ارائه همه اطلاعات لازم بصورت کتبی و شفاهی
- زبان قابل فهم ودرک برای شرکت کننده
- امکان پرسیدن سئوالات
- آزادی در تصمیم گیری
- فرصت تصمیم گیری
- اخذ رضایت مکتوب

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رضایت آزادانه

- آزادی در عمل
- ترس از رنجش
- ترس از دریافت درمان ناکافی
- انگیزه مالی نامتعارف
- اعمال نفوذ

Informed consent form(ICF)
فرم رضایت آگاهانه

- کسب رضایت آگاهانه یک فرایند گفتگو بین محقق و شرکت کننده در مطالعه است که در فرم رضایت آگاهانه مستند می شود.
- این مستند یکی از مهمترین مستندات آغاز مطالعه کارآزمایی بالینی است که باید وجود، محتوا و استفاده از آن باید مورد تایید کمیته اخلاق ذی ربط قرار بگیرد.

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اجزاء برگه اطلاعات

۱. این یک مطالعه تحقیقاتی است.
۲. اهداف مورد نظر تحقیق
۳. درمانهایی که در این کارآزمایی وجود دارد و اینکه افراد به طور تصادفی به هر یک از گروههای درمانی وارد میشوند.
۴. روش‌های پی‌گیری شامل روش‌های تهاجمی و غیرتهاجمی
۵. نحوه همکاری شرکت کننده
۶. تشریح خطرات قابل پیش بینی مطالعه برای شرکت کنندگان
۷. فوائد احتمالی مطالعه برای شرکت کنندگان. اگر مطالعه فایده مستقیمی برای شرکت کنندگان ندارد, باید از این موضوع آگاه گردند.

اجزاء برگه اطلاعات

۸. سایر درمانهای موجود و فواید و خطرات هر یک از آنها.

۹. غرامت و درمان صدماتی که در جریان مطالعه به فرد وارد میشود.

۱۰. در صورتیکه مخارجی که شرکت کننده برای شرکت در مطالعه متحمل میشود بازپرداخت میشود، نحوه آن ذکر شود.

۱۱. در صورتیکه وجهی در قبال شرکت وی در مطالعه پرداخت میشود میزان و نحوه آن ذکر شود

۱۲. شرکت در مطالعه داوطلبانه است و میتوانند از شرکت امتناع ورزد و یا هر زمان مایل بود از مطالعه خارج شود بدون آنکه مشمول پرداخت جریمه گردد و یا از خدمات درمانی محروم شود.

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اجزاء برگه اطلاعات

۱۳. نگهداری محرمانه اطلاعات فرد شرکت کننده و اینکه در انتشار نتایج هویت افراد شرکت کننده محرمانه خواهد ماند.

۱۴. فرد شرکت کننده در طول مطالعه از اطلاعاتی که ممکن است بر تصمیم وی در مشارکت در مطالعه تاثیر بگذارد مطلع خواهند شد.

۱۵. فرد یا افرادی که شرکت کننده برای دانستن حقوق خود،کسب اطلاعات بیشتر و یا در موقع صدمه از مطالعه میتواند با وی تماس بگیرد.

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اجزاء برگه اطلاعات

۱۵. طول تخمینی دوره همکاری شرکت کننده در مطالعه.

۱۶. تعارض منافع احتمالی پژوهشگران

۱۷. حق دسترسی کمیته اخلاق به اطلاعات مربوط به بیماران با رعایت رازداری

اخذ رضایت از افراد بی سواد

- اگر فرد شرکت‌کننده یا نماینده قانونی وی قادر به خواندن رضایت‌نامه نباشد، باید یک فرد با سواد و بیطرف در جریان توضیحات فرم رضایت‌نامه حضور داشته باشد.
- بعد از اینکه فرد شرکت کننده یا نماینده قانونی وی شفاهاً با انجام کارآزمایی موافقت نمود، باید فرم رضایت‌نامه را امضاء (یا اثر انگشت خود را درج نمایند) نماید.
- فرد بیطرف نیز باید فرم رضایت‌نامه را امضاء و تاریخ را ثبت کند. فرد با سواد و بیطرف باید گواهی نماید که اطلاعات فرم رضایت‌نامه بطور دقیق برای شرکت‌کننده یا نماینده قانونی وی توضیح داده شده و رضایت آزادانه از این افراد اخذ گردیده است .

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اصل خیررسانی

- ضرر و زیان می تواند جسمی، اجتماعی و روانی باشد
- شرکت کنندگان در پژوهش در معرض خطری بیش از حداقل لازم، قرار نمی‌گیرند
  - در پژوهش های درمانی روش مورد استفاده نباید برای بیمار زیانی بیش از درمان یا آزمایش معیار و پذیرفته شده داشته باشد.
  - در پژوهش های غیر درمانی شرکت در پژوهش نباید برای شرکت کننده خطری بیشتر از خطرات معمولی که طی فعالیت‌های روزانه با آن روبروست، در پی داشته باشد.
- منفعتی که آزمودنی به دست می آورد باید بیشتر از خطری باشد که ممکن است با آن مواجه شود
- موازنه مثبت منفعت به ضرر نیازمند آگاهی پژوهشگر از میزان و نوع خطر، و سودرسانی های پژوهش برای آزمودنی است
- پژوهشگر باید با توجه به علم روز به همه خطرها و منافع آگاهی داشته باشد
- تصمیم گیری در خصوص میزان خطر قابل توجیه با کمیته اخلاق می‌باشد.
- صرف رضایت آگاهانه بیمار برای پذیرش خطر، تحمیل خطر اضافی را توجیه نمی کند

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کمینه سازی خطر /بیشینه سازی منفعت

- برقراری نظام پایش
- معیارهای خروج از پژوهش
- مشخص کردن گروههای آسیب پذیر
- روش دستیابی به رمزهای کورسازی مطالعه در موارد فوریت
- روشهای مناسب برای جلوگیری از افشای راز آزمودنی
- استفاده از آزمودنی هایی که احتمال سودبردن آنان بیشتر است.
- استفاده از بهترین روش های مراقبتی، تشخیصی و درمانی در پژوهش
- کارآزمایی بالینی باید تنها توسط افراد دارای مجوز حرفه‌ای مرتبط و ذی‌صلاح از نظر علمی انجام گیرد
- ..

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اصل عدالت(justice)

- انتخاب گروههای افراد باید فقط « مبنای علمی» داشته باشد.
- توزیع عادلانه سختی ها، زیان ها، و منافع پژوهش در گروههای گوناگون آزمودنی است
- بیشترین کاربرد اصل عدالت در انتخاب آزمودنی است
- امکان استفاده از گروه های آسیب پذیر در پژوهش، به علت پایگاه ضعیف اجتماعی شان، بیشتر شده و در نتیجه زیان مطالعه ها به سوی گروه های آسیب پذیر متوجه شده است؛ اما گروه های عادی اجتماعی از نتیجه پژوهشها سود می برند.

باید تأکید کرد که ارتقای عدالت مستلزم محافظت از گروه های آسیب پذیر در برابر زیان های ناشی از پژوهش ها است.

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کمیته های اخلاق در پژوهش

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وظایف کمیته های اخلاق در پژوهش

- ارزیابی مستقل
- کمیته اخلاق وظیفه حفاظت از حقوق, ایمنی و رفاه افراد شرکت کننده در طرح را بعهده دارد
- حیطه مسئولیت این کمیته بر حسب معیارهای اخلاقی و فرهنگی کشورهای گوناگون متفاوت است
- بازنگری علمی و اخلاقی

اجزای مورد بررسی طرحها

- خطر برای شرکت کنندگان در پژوهش در حداقل ممکن باشد.
- پژوهشگران صلاحیت علمی انجام پژوهش را داشته باشند.
- خطر برای شرکت کنندگان در پژوهش به نسبت سودمندی که مطالعه برای وی دارد و دانشی که در اثر انجام مطالعه حاصل می‌شود قابل دفاع باشد.
- انتخاب نمونه‌ها عادلانه باشد.
- رضایت آگاهانه از تمام افراد مورد پژوهش یا نماینده قانونی آن‌ها اخذ گردد.
- حداکثر رعایت رازداری از داده‌های پژوهش به عمل آید.
- وقتی پژوهش حسب ضرورت بر روی افراد آسیب‌پذیر انجام می‌شود، اقدامات مورد لزوم در حفاظت از حقوق و آسایش آن‌ها به عمل آید.

پرداخت غرامت

- هر گونه خسارت وارده به آزمودنی که ناشی از مشارکت او در کارآزمایی باشد، به‌نحوی که اگر فرد وارد مطالعه نمی‌شد چنین اتفاقی برای وی رخ نمی‌داد، باید به‌نحو مناسب جبران شود.
- در دستورالعمل کارآزمایی و فرم رضایت آگاهانه باید مشخص شود که مسؤول پرداخت غرامت چه فرد یا سازمانی است.(شرکت داروسازی، پژوهشگر و موسسه مربوطه)
- در صورت مشخص نشدن این مورد، مجری اصلی کارآزمایی مسؤول جبران خسارت وارده و پرداخت غرامت است.
- جبران خسارت وارده به آزمودنی در کارآزمایی‌های بالینی در هر صورت باید جبران شود و مشروط به احراز تقصیر پژوهشگر نیست.

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پایان

Adverse Events in Clinical Trials

Mansour Shamsipour

Epidemiologist

Clinical Trial Center

Tehran University of Medical Sciences

shamsipour@sina.tums.ac.ir

Evaluating New Interventions
Safety Is Not Optional

- Clinical development is not just about does it work? — but is it safe?
- The **assessment** is generally asymmetric

Efficacy	Safety
Does the intervention achieve its intended **therapeutic effect?**	Does it cause harm that outweighs its benefit?
Measured by: Response rates, survival, biomarkers	Measured by: Adverse Events (AEs), SAEs, SUSARs
Drives Initial approval	Drives patient trust, regulatory acceptance, and long-term use

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AE,AR

رخداد نامطلوب (Adverse Event – AE)

- **تعریف:** هر رخدادی پزشکی نامطلوب که در طول مطالعه یا پس از دریافت درمان رخ می‌دهد، **بدون توجه به اینکه علت آن دارو یا مداخله باشد یا نه**.

عارضه جانبی (Adverse Reaction -AR)

- **تعریف**: رخداد نامطلوبی که به احتمال زیاد ناشی از دارو یا مداخله باشد.
- ویژگی‌ها: ارتباط علت و معلولی با درمان مشخص یا محتمل است.

خلاصه:

- AE
- هر مشکل پزشکی که رخ می‌دهد (علت مشخص نیست)
- AR
- مشکلی که دارو یا مداخله باعث آن شده است

Adverse Events in Clinical Trials

- There is no perfectly Safe intervention
- All treatments result in some adverse events
- What and how to collect these data, assessment ,analysis, report ?

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Presentation Objectives

- Importance of Adverse Events
- Define and differentiate AE, SAE,
- Global standard for Classification adverse event
- MedDRA
- Use CTCAE v5.0 to accurately grade AE severity
- Understand regulatory reporting

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Importance of Adverse Events (AEs) in Clinical Trials

- AEs are the earliest warning signals of potential drug risks.
- Even non-serious AEs can reveal hidden toxicity patterns, especially in vulnerable populations.
- Incomplete or delayed AE **reporting** can lead to:
  - Patient harm
  - Trial suspension or termination
  - Regulatory penalties or market withdrawal

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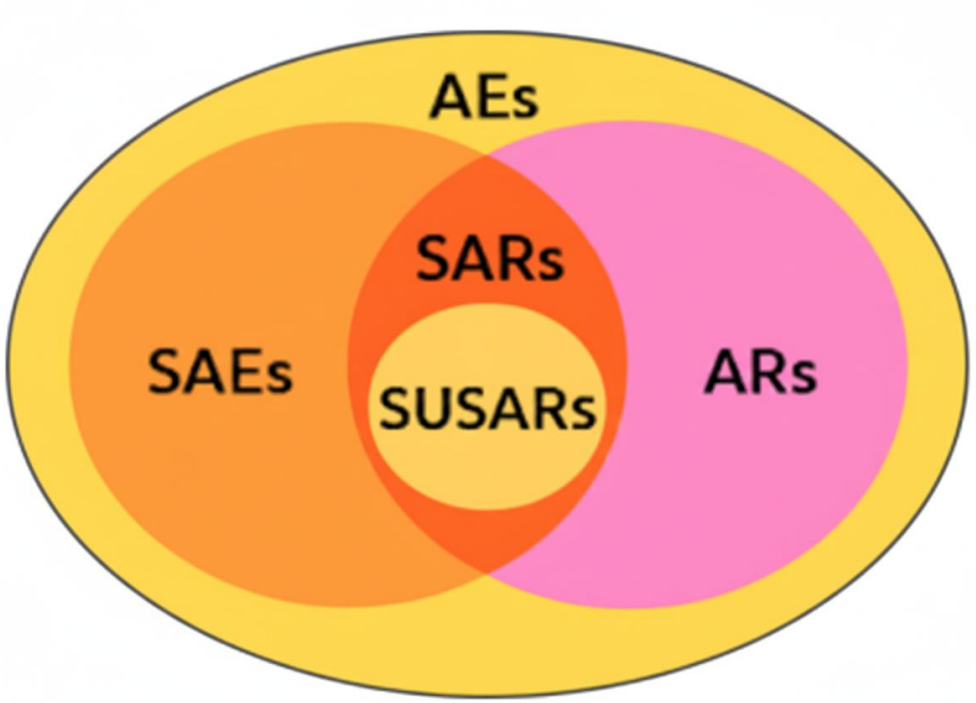
Definitions



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AE,AR

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- **تعریف:** هر رخدادی پزشکی نامطلوب که در طول مطالعه یا پس از دریافت درمان رخ می‌دهد، **بدون توجه به اینکه علت آن دارو یا مداخله باشد یا نه**.

عارضه جانبی (Adverse Reaction -AR)

- **تعریف**: رخداد نامطلوبی که به احتمال زیاد ناشی از دارو یا مداخله باشد.
- ویژگی‌ها: ارتباط علت و معلولی با درمان مشخص یا محتمل است.

خلاصه:

- AE
- هر مشکل پزشکی که رخ می‌دهد (علت مشخص نیست)
- AR
- مشکلی که دارو یا مداخله باعث آن شده است

Suspected Unexpected Serious Adverse Reaction

- یک **واکنش نامطلوب جدی** که:
- **مورد مشکوک به ارتباط با دارو/مداخله** باشد (**Suspected**)
- **غیرمنتظره** باشد (یعنی در اطلاعات دارویی قبلی یا برچسب دارو ذکر نشده یا شدت آن بیشتر از انتظار باشد) **Unexpected**
- **جدی** باشد **Serious**
- جدی یعنی منجر به مرگ، تهدید حیات، بستری شدن، نقص دائمی یا عارضه مهم پزشکی شود.
- **مثال SUSAR**
- بیمار در کارآزمایی فاز ۲ یک داروی جدید ضدسرطان دچار آنافیلاکسی شدید (واکنش آلرژیک تهدیدکننده زندگی) می‌شود.
- چنین واکنشی جدی است، غیرمنتظره است (در مطالعات قبلی یا لیبل دارو گزارش نشده)، و احتمالاً مربوط به دارو است SUSAR محسوب می‌شود.

Classification of Adverse Events

- زمین دور سرم میچرخه، احساس سبکی سر، چشام را نمی تونم باز نگهدارم (اصطلاحات فرهنگی خاص)
- Ensures **consistency across sites, countries**, and databases for global safety analysis.
- Why MedDRA?
- MedDRA (Medical Dictionary for Regulatory Activities)
- The global standard for Classification adverse event
- Categorized term for sign, symptom, disease, diagnoses,
- **Easy of use for** :data entry, analysis, display

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MedDRA
Medical Dictionary for Regulatory Activities

MedDRA

- Developed by ICH
- Used by FDA, EMA, WHO, and ,.
- 5-Level Hierarchical Structure:
- SOC (System Organ Class)
- PT (Preferred Term: single medical concepts)
- Used for reporting (Dizziness, Palpitations,..)
- Example:
- "Cough" → PT: Cough
- **SOC**: Respiratory, Thoracic and Mediastinal Disorders

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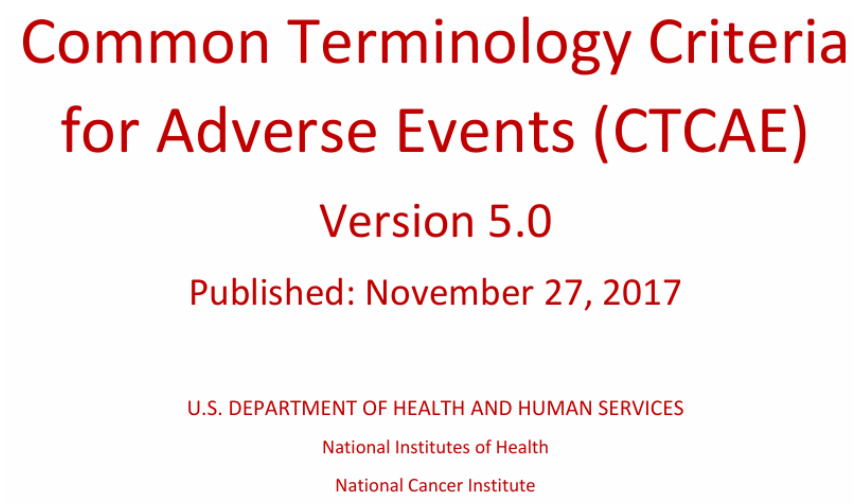
Measuring Severity – CTCAE v5.0

- CTCAE (Common Terminology Criteria for Adverse Events) v5.0
- Five step severity scale
- The gold standard for grading AE severity (especially in oncology).



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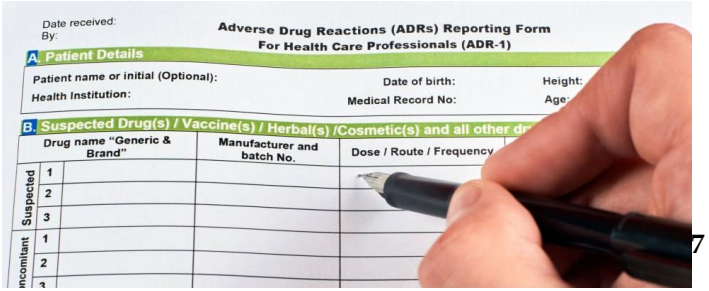
CTCAE

Grade	Description
1-Mild خفیف	Asymptomatic or mild symptoms; no intervention needed بدون علامت یا با علائم خفیف؛ نیاز به مداخله ندارد
2-Moderate متوسط	Limits instrumental ADL; oral meds/intervention محدودکننده فعالیت‌های روزمره نیازمند دارو یا مداخله خوراکی
3-Severe شدید	Limits self-care ADL; requires IV fluids/hospitalization محدودکننده فعالیت‌های روزمره مربوط به مراقبت از خود نیازمند مایعات وریدی یا بستری
4-Life-threatening تهدید کننده حیات	Urgent intervention required (e.g., ICU) نیازمند مداخله فوری (مثلاً مراقبت ویژه/ICU)
5-Death مرگ	Fatal outcome پیامد مرگبار



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CTCAE + MedDRA

- 📌 CTCAE + MedDRA = Complete Picture
- MedDRA tells you what happened.
- CTCAE tells you how bad it was.

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Causality Assessment in Adverse Events

- What Is Causality Assessment?
- The clinical judgment that answers:
- "Is this adverse event likely caused by the study drug?"
- Performed by: Investigator at the site
- **Required for**:
- Classifying AE ⟶ Adverse Reaction
- Identifying SUSARs
- Deciding on dose modification or trial hold

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How Is It Done? 5 Key Factors

Factor	Description
1. Temporal Relationship	Did the AE occur after drug exposure? Is the timing plausible? آیا عارضه پس از دریافت دارو رخ داده است؟ آیا زمان‌بندی آن منطقی و قابل قبول است؟
2. Dechallenge	Did the AE improve after stopping the drug? آیا پس از قطع دارو، عارضه بهبود پیدا کرد؟
3. Rechallenge(Rare)	Did the AE return when the drug was restarted? (Ethically avoided) آیا با شروع مجدد دارو، عارضه دوباره ظاهر شد؟ (از نظر اخلاقی معمولاً انجام نمی‌شود)
4. Alternative Causes	Could it be due to disease, other meds, infection, or comorbidities? آیا ممکن است علت عارضه بیماری زمینه‌ای، داروهای دیگر، عفونت یا هم‌ابتلایی‌ها باشد؟
5. Known Pharmacology	Is this AE consistent with the drug's mechanism or class? (Check IB!) آیا این عارضه با مکانیسم یا رده دارویی شناخته‌شده سازگار است؟

No single factor is decisive — the investigator integrates all evidence.

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Common Causality Categories

Term	Meaning
Related	Strong evidence of drug causality شواهد قوی از علیت دارو وجود دارد
Probably Related	Good evidence, but not definitive شواهد خوب وجود دارد، اما قطعی نیست
Possibly Related	Plausible, but other causes possible ارتباط محتمل است، اما علل دیگر هم قابل‌قبول هستند
Not Related	Clear alternative cause (e.g., trauma, infection) علت واضح و جایگزین وجود دارد (مثلاً تروما، عفونت)
Uncertain / Unknown	Insufficient data — requires follow-up اطلاعات ناکافی است — نیاز به پیگیری دارد

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Tools for Collecting Adverse Events

- Objective: Systematically identify, document, and monitor all adverse events (AEs) and serious adverse events (SAEs).
- **Key Tools:**

- Standardized AE grading scales (e.g., CTCAE, MedDRA terminology)
- Patient diaries (electronic or paper-based)
- Structured AE/SAE reporting forms
- Scheduled, protocol-driven patient interviews
- Routine clinical assessments & laboratory monitoring
- Electronic Data Capture (EDC) systems with built-in safety flags

Dimensions

واقعه ناخواسته بعد از تزریق وجود داشته است؟ بله□ خیر□ در صورتی که پاسخ "بله" است جدول زیر تکمیل گردد.

گزارش وقایع ناخواسته (ویزیت ۱: روز ۰)

توصیف رخداد		تاریخ وقوع mm/dd/	تاریخ خاتمه mm/dd/	شدت	رابطه علیتی	جدیت عارضه Non-serious = 0 Serious = 1 (در صورت وقوع SAE فرم مربوطه را تکمیل نمایید)	اقدام در مورد داروی مطالعه None=0 Temporarily drug discontinuation =1 Permanently drug discontinuation =2 Withdrawn from the trial=3 Other=4* *Specify:	سایر درمان ها None=0 Medication treatment =1 Non-medication treatment =2* *Specify: Hospitalisation =3 Other=4** **Specify:	نتیجه ۰- Recovered ۱- Recovering ۲- Not recovered ۳- Recovered with sequelea ۴- Death ۵- Unknown
SOC Central nervous system	PT Headache	__/__/__	__/__/__	__	.....	__	__	__	__
	Dizziness	__/__/__	__/__/__	__	.....	__	__	__	__
	Syncope	__/__/__	__/__/__	__	.....	__	__	__	__

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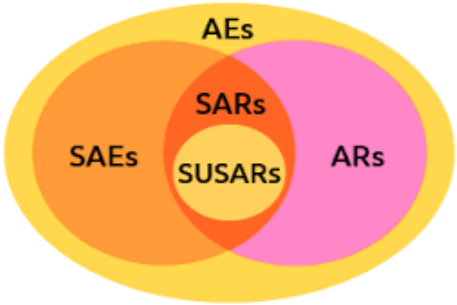
بررسی گزارشات ایمنی طی اجرای مطالعات بالینی

- گزارش فوری رخدادهای نامطلوب جدی (SAEs& SUSARs):
  - رخداد نامطلوب شدید (منجر به مرگ یا قرار گرفتن در معرض خطر مرگ
  - ظرف ۲۴ ساعت توسط مجری به اسپانسر و کمیته اخلاق (به طریق مقتضی)
  - رخداد نامطلوب شدید (مداخلات درمانی، جراحی و..)
  - حداکثر ظرف ۷ روز توسط مجری به اسپانسر و کمیته اخلاق (به طریق مقتضی)
  - ۱۵ روز تقویمی توسط اسپانسر به اداره کل دارو در قالب فرم CIOMS

- Council for International Organizations of Medical Sciences (CIOMS)



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Key Takeaways

- Always:
- Record ALL AEs, even if mild or unrelated
- Use MedDRA PTs for consistent coding
- Apply CTCAE v5.0 to grade severity
- Key Tools (CRF, Diary Card, telephone, Expert)
- Timely Reporting

Essential Documents in Clinical Trials

Mansour Shamsipour

Epidemiologist

Clinical Trial Center

Tehran University of Medical Sciences

shamsipour@sina.tums.ac.ir

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Objectives

- Define essential documents and their role in clinical trials
- What Is the Trial Master File ?
- Minimum list of Eds?

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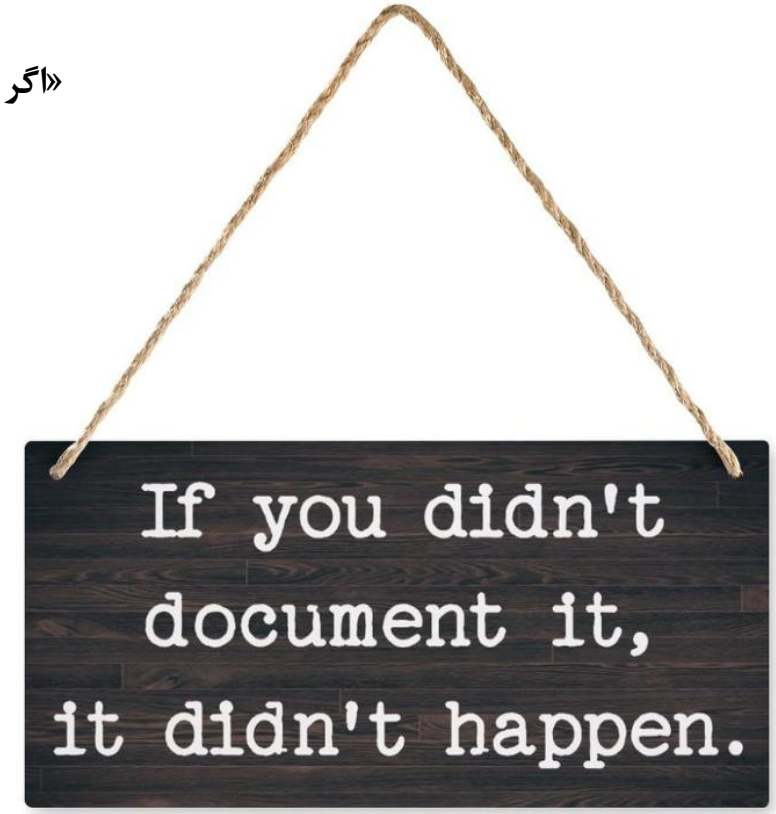
ICH-GCP

«اگر ثبت نکردی، اتفاق نیفتاده است.»
(اصل بنیادی در رعایت GCP)



It's not just a saying — it's a regulatory and ethical requirement

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Definition: ICH - Guidance

- Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

چگونه به ارزیابی کمک می‌کند؟	سند ضروری
• نشان می‌دهد که هدف، روش و معیارهای ورود/خروج چه بوده است.	پروتکل مطالعه
• اثبات می‌کند که شرکت‌کنندگان به‌صورت آگاهانه و داوطلبانه وارد مطالعه شده‌اند.	فرم رضایت آگاهانه
• نشان می‌دهد که ایمنی شرکت‌کنندگان چگونه پایش شده است.	گزارش عوارض جانبی
• منبع اصلی داده‌های تحلیل‌شده در نتایج مطالعه است.	فرم گزارش مورد (CRF)
• نشان می‌دهد که آیا مطالعه به‌درستی پیگیری و کنترل شده است یا خیر.	گزارش بازدید نظارتی Monitoring Visit Report

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Key Purposes

- Prove compliance with GCP and ethical standards (investigator/institution and sponsor/Monitor)
- Enable reconstruction of trial events
- Support Audit and regulatory inspections (FDA, EMA, etc.)
- Document accountability and trial conduct for long-term retention
- Critical for data credibility and subject protection
- Missing one document can invalidate months of work.

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What Is the Trial Master File (TMF)?

- Definition:
- A structured collection of all essential documents demonstrating that the trial was conducted in accordance with GCP and the approved protocol.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

06 December 2018
EMA/INS/GCP/856758/2018
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)

No TMF = No approval. Incomplete TMF = Delayed approval.

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Minimum list of EDs

- The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated:
- - Before the clinical phase
- - During clinical conduct
- - After completion/termination of trial
- According to the file type
- - Investigator
- - Sponsor/CRO

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Content of a TMF – Before the Clinical Phase

No.	Document	Sponsor/CRO File	Investigator File	Third Party File
1	Investigator Brochure	✓	✓	
2	Signed Protocol + Amendments + Sample CRF	✓	✓	
3	Informed Consent Forms (+ translations) + Other Written Information	✓	✓	
4	Advertisements, if applicable	X	✓	
5	Financial Agreement	✓	✓	
6	Insurance, if applicable		✓	
7	Agreements – Sponsor/CRO/Site/Institution	✓	✓	
8	Ethics Committee Approval	✓	✓	
9	Ethics Committee Composition/Constitution	✓ (where required)	✓	
10	Regulatory Authority Approval/Notification	✓ (where required)	✓	
11	CVs	✓	✓	
12	Laboratory/Medical/Technical – normal ranges	✓	✓	
12	Laboratory/Medical/Technical – certification, accreditation, QC	✓	✓ (where required)	
13	IMP Sample Labels	✓	X	
14	IMP Handling	✓	✓	
15	IMP Distribution	✓	✓	
16	Certificates of Analysis	✓	✓	
17	Decoding Procedure	✓	✓	?

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During clinical conduct

No.	Document	Sponsor/CRO File	Investigator File	Third Party File
14	Completed CRFs	✓ (original)	✓ (copy)	
15	CRF Corrections	✓ (original)	✓ (copy)	
16	SAE Reports	✓	✓	
17	SUSAR + Other Safety Reports	✓	✓ (where required)	
18	Safety Information to Investigator	✓	✓	
19	Interim/Annual Reports to Ethics Committee and Regulatory Authority	✓ (where required)	✓	
20	Subject Screening Log	✓	✓ (where required)	
21	Subject ID List	X	✓	
22	Subject Enrolment List	X	✓	
23	IMP Accountability	✓	✓	
24	Signature Sheet	✓	✓	
25	Record of Retained Body Fluids/Tissue Samples	✓	✓	

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During clinical conduct

No.	Document	Sponsor/CRO File	Investigator File	Third Party File
1	Investigator Brochure updates	✓	✓	
2	Revision to Protocol + Amendments + Informed Consent Forms + other written information	✓	✓	
3	Ethics Committee Approval	✓	✓	
4	Regulatory Authority Approval/Notification	✓	✓ (where required)	
5	New CVs	✓	✓	
6	Updates Laboratory/Medical/Technical – normal ranges		✓	
7	Updates Laboratory/Medical/Technical – certification, accreditation, QC	✓	✓ (where required)	
8	IMP/Study Materials Destruction	✓	✓	
9	Certificates of Analysis for any new batches	✓	X	
10	Monitoring Visit Reports	✓	X	
11	Relevant Communications	✓	✓	
12	Signed Informed Consents	X	✓	
13	Source Documents	X	✓	

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Content of a TMF – At Completion/Termination

No.	Document	Sponsor/CRO File	Investigator File	Third Party File
1	IMP Accountability	✓	✓	
2	IMP Destruction	✓	✓ (if destroyed at site)	
3	Subject ID Code list	X	✓	
4	Audit Certificate, if applicable	✓	X	
5	Final Closeout Monitoring Report	✓	X	
6	Treatment Allocation & Decoding Documents	✓	X	
7	Final Report by Investigator to Ethics Committee and Regulatory	X	✓	
8	Clinical Study Report	✓	✓ (if applicable)	

Top Essential Documents

Document	Purpose	Risk if Missing
Protocol	Study blueprint	Invalidates entire trial
IB (Investigator's Brochure)	Safety profile of IP	Compromises subject safety
ICF (Informed Consent Form)	Proof of voluntary participation	Ethical violation
CRF / eCRF	Structured data capture	Data integrity issues
Source Data	Original record of observations	"No source = no data"
IP Accountability Log	Track investigational product	Loss, misuse, diversion
Monitoring Reports	Evidence of oversight	Lack of quality control

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Case Report Form (CRF)

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Case Report Form (CRF)

- **Definition:**
  A printed, optical, or electronic document designed to capture all protocol-required data for each trial participant to be reported to the sponsor.
- **Key Importance:**
- Primary tool for collecting, organizing, and transmitting trial data
- Foundation for statistical analysis and clinical study reports (CSRs)
- Enables data quality control, monitoring, and audit readiness
- Essential component of the Trial Master File (TMF)
- Protocol should specify which CRF fields serve as source data (e.g., patient surveys,

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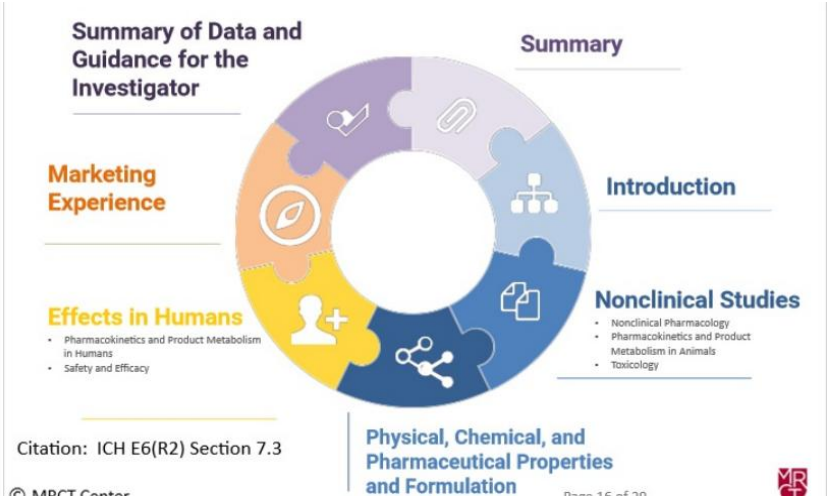
Investigator's Brochure (IB)

- **Definition:**

A comprehensive, up-to-date summary of all relevant nonclinical and clinical data on the investigational product(s), prepared by the sponsor and provided to investigators.



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Investigator's Brochure (IB)

- **Key Content Includes**:
- Chemical, pharmaceutical, and pharmacological properties
- Nonclinical toxicology and pharmacokinetic data
- Results of prior clinical trials (efficacy & safety)
- Known and potential risks, adverse reactions, and contraindications Dosage, administration, and handling instructions

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Source Documents are Essential Documents

- Source documents :"*All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial."*
  - They verify, or document, the existence of the participant and integrity of the data collected about the participant.
- Source Data is the information in the original records and certified copies of original records of clinical findings, observations or other activities in a study, enabling one to:
  - Reconstruct a study
  - Confirm the participant existed
  - Evaluate data integrity

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Examples

Medical Records

Lab Reports

X-Rays, ECGs

Intake / Screening Forms

Telephone Contact Records, Faxes, email

Subject Diaries

Informed Consent Forms

Drug Disposition Records

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Quality of source documents

- The investigator and institution are responsible for maintaining source documents and trial records that include all relevant observations on each of the site's trial participants.

- Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary

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Quality of source documents

- Sponsors, Monitors, and Investigators frequently refer to the ALCOA-C system of source documentation.
  - Attributable: It should be clear who documented the data
  - Legible: The data should be readable and signatures should be identifiable
  - Contemporaneous: The data should be or dated in the correct time frame as compared to the flow of events in the trial.
  - Original: The data should be the first documentation of the record made, or the original source data.
  - Accurate: The data should be a real representation of facts
  - Complete: The data should be complete up to the point in time that the source data is being reviewed. The information should be complete (i.e., to answer who, what, when, where, why, and how).

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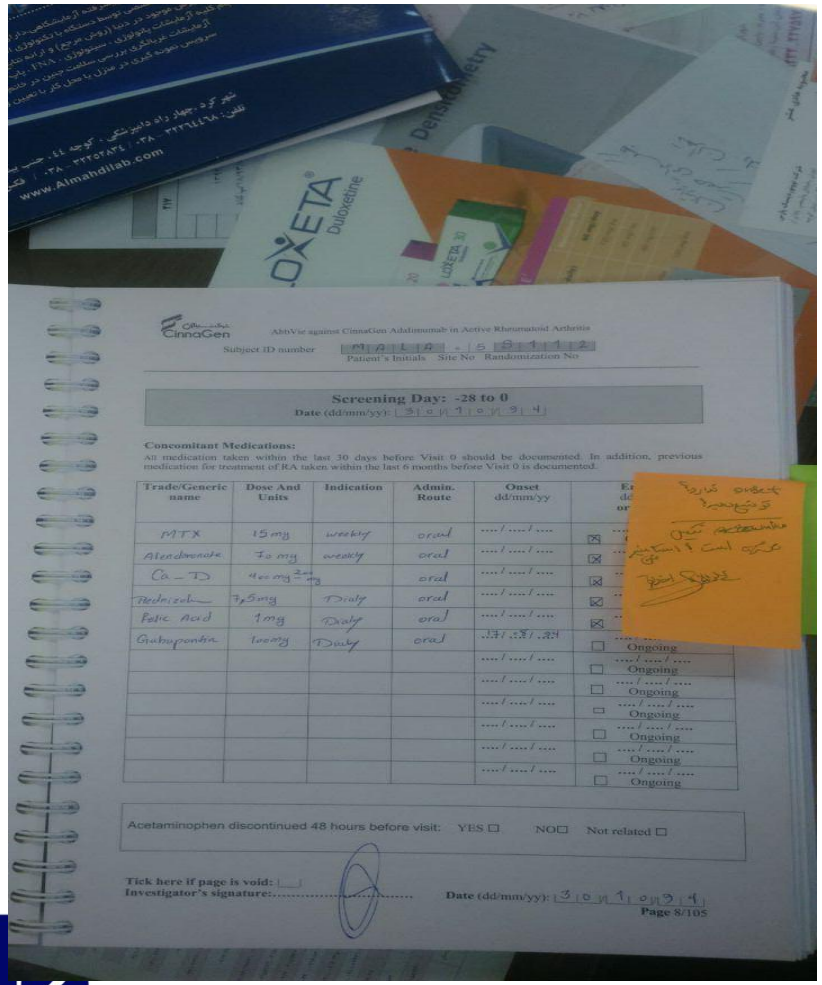
CRF, source documents



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Location of essential documents

- Investigators and Sponsors should maintain the location of all essential documents, including source documents.
- At all times (before, during and after the trial), the Investigator and Institution should maintain control of all essential documents generated at the site.

- In advance of trial initiation, essential documents can be added, enhanced, or reduced based on the documents importance and relevance to the trial.
- Regardless of whether a paper-based or electronically-based system is used, the document storage system should allow for each document to be identified, searched, and retrieved.
- Version history should be identified with each document.

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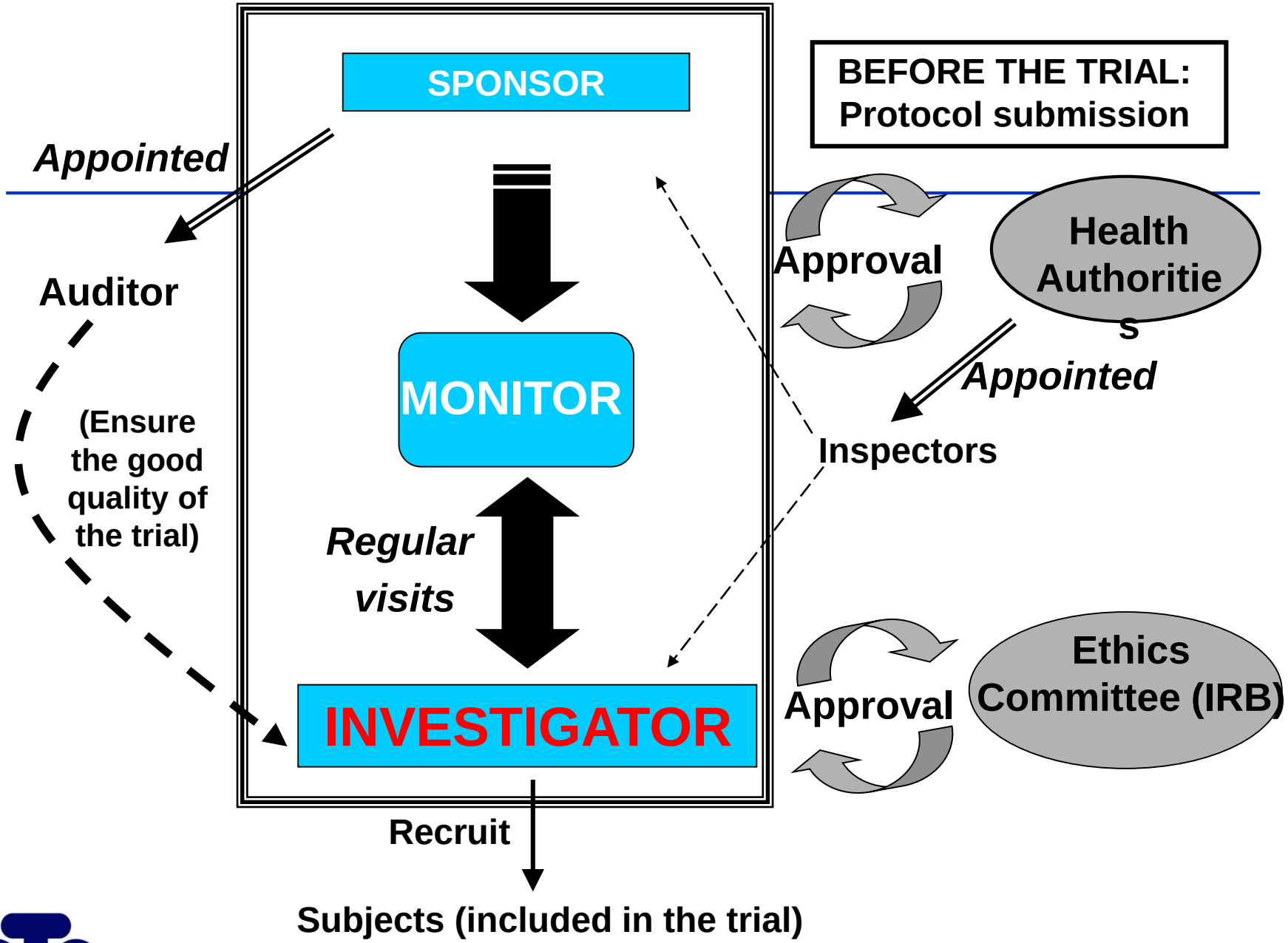
Summary


Essential documents allow
• a third party to review and understand what occurred in the study
• for a traceable audit trail of each participant
Source documentation is the first place data is recorded.
• ALCOA-C principles should be followed when documenting trial data
Investigators should
• have control over the data
• document the location where data are stored


SPONSOR
BEFORE THE TRIAL:
Protocol submission
Appointed
Auditor
(Ensure the good quality of the trial)
Approval
Health Authorities
Appointed
Inspectors
MONITOR
Regular visits
INVESTIGATOR
Approval
Ethics Committee (IRB)
Recruit
Subjects (included in the trial)

Investigator Responsibilities

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Investigator

- **Who is Investigator?**

- A person responsible for the conduct of the clinical trial at a trial site.
  - The location(s) where trial-related activities are actually conducted.
- If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called as Principal Investigator **PI**.
- Chief Investigator **CI**

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What's the Difference?

Clinical Practice

VS

Clinical Research

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What's the Difference?

- Clinical investigators face challenges during the conduct of clinical trials that are distinctly different from those encountered during the routine practice of medicine.

- Many of these challenges stem from regulatory requirements, the Guidelines for Good Clinical Practice (GCP) and the rigorous nature of clinical trials.

- A clinical research study is a scientific experiment and all activities are held to a higher standard than routine clinical practice.

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Sub-investigator

- **Conduct study activities delegated by Investigator**
  - Prepare IRB documents
  - Recruit patients
  - Obtain informed consent
  - Complete accurate regulatory documentation
  - Conduct study activities with subject
  - Maintain accurate drug accountability

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Investigator Responsibilities

The Investigator is ultimately responsible for all study-related activities at his or her site, regardless of who has been delegated the various study responsibilities

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Section 4.0 Investigator Responsibilities

4.1 Investigator's Qualifications and Agreements	4.8 Informed Consent of Trial Subjects
4.2 Adequate Resources	4.9 Records and Reports
4.3 Medical Care of Trial Subjects	4.10 Progress Reports
4.4 Communications with IRB/IEC	4.11 Safety Reporting
4.5 Compliance with Protocol	4.12 Premature Termination or Suspension of a Trial
4.6 Investigational Product(s)	4.13 Final Report(s) by Investigator
4.7 Randomization Procedures and Unblinding	All local and country-level requirements must also be met.

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Qualifications and Agreements

- The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial.
  - Should meet all the qualifications specified by the applicable regulatory requirement(s).
  - Should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation.

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Qualifications and Agreements

- Be thoroughly familiar with the appropriate use of the investigational product(s) as described in the protocol ,IB ,……
- Aware of, and should comply with, GCP and the applicable regulatory requirements.
- Permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

- Maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

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Adequate Resources

- The investigator should
  - be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
  - have sufficient time to properly conduct and complete the trial within the agreed trial period.
  - have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial
  - ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

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Medical Care of Trial Subjects

- A qualified physician should be responsible for all trial-related medical decisions.

- During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events.

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Communication with IRB/IEC

- Before initiating a trial, the investigator should have:
  - Written and dated approval from the IRB/IEC for the trial protocol
  - Written informed consent form
  - Any other written information to be provided to subjects.
- The investigator should provide the IRB/IEC with a current copy of the Investigator's Brochure.
- During the trial the investigator should provide to the IRB/IEC all documents subject to review.

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Compliance with Protocol

- Conduct the study according to protocol

- The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval from the IRB/IEC of an amendment.

  - Except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s))

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Compliance with Protocol

- The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
- As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:
  - to the IRB/IEC for review and approval
  - to the sponsor for agreement and, if required,
  - to the regulatory authority(ies).

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Investigational Product(s)

- The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).
- The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.
- The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check that each subject is following the instructions properly.

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Storage condition

VS

Randomization and Unblinding

- The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol.

- If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

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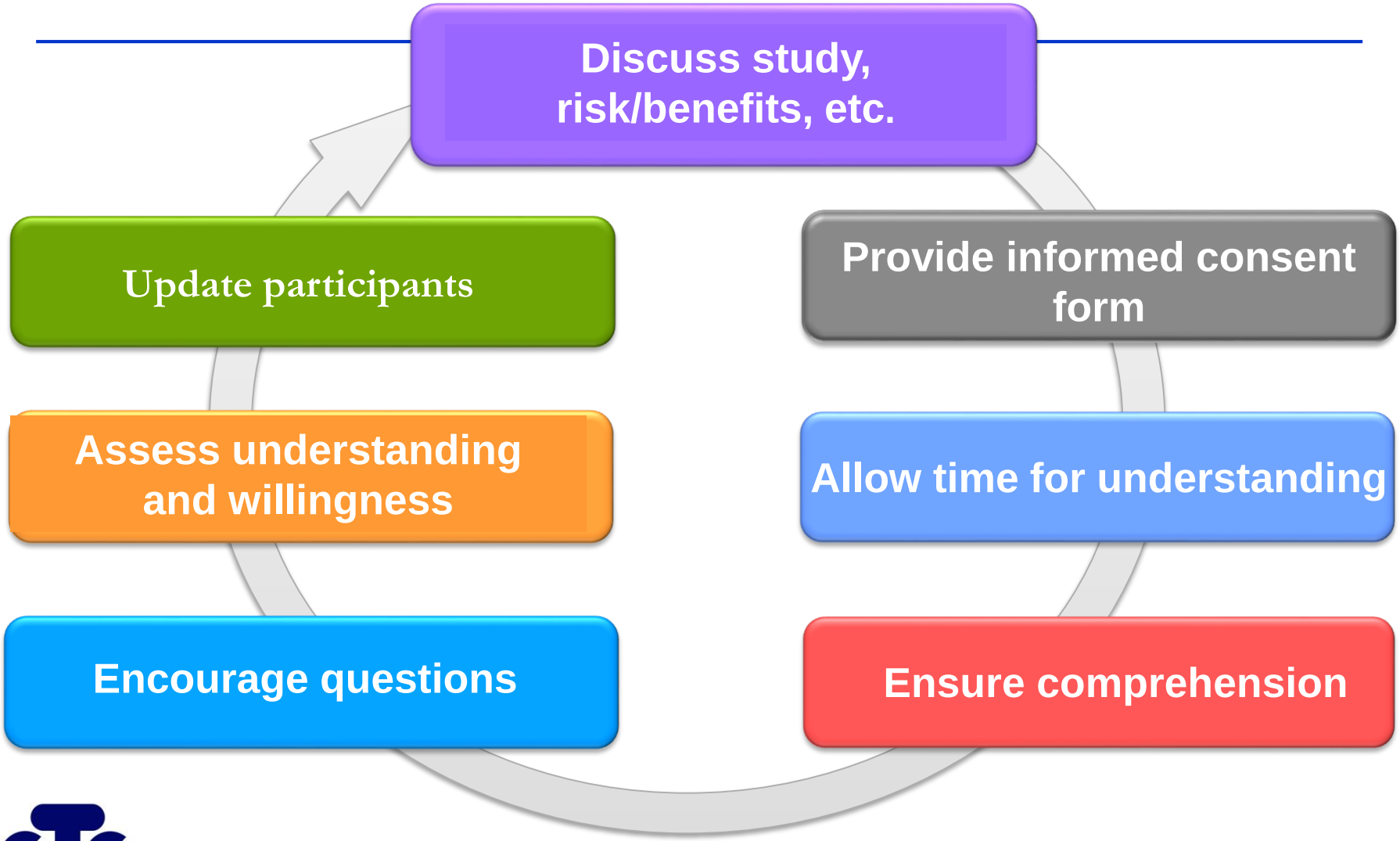
Informed Consent of Study Subjects

- Provide IRB/IEC approved written informed consent form to subject
- Language of informed consent form should be nontechnical and understandable to the subject
- Subject should be given ample time and opportunity to ask questions
- Subject should sign and personally date informed consent form prior to initiation of study procedures

The Consenting Process



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Records and Reports

- The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

- Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

- The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s).

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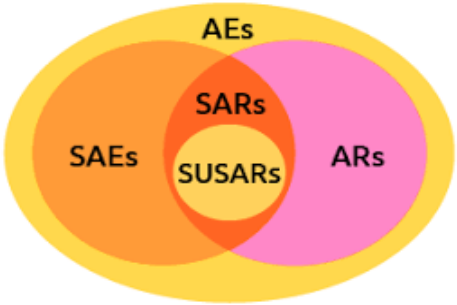
بررسی گزارشات ایمنی طی اجرای مطالعات بالینی

- گزارش فوری رخدادهای نامطلوب جدی (SAEs& SUSARs):
  - رخداد نامطلوب شدید (منجر به مرگ یا قرار گرفتن در معرض خطر مرگ
  - ظرف ۲۴ ساعت توسط مجری به اسپانسر و کمیته اخلاق (به طریق مقتضی)
  - رخداد نامطلوب شدید (مداخلات درمانی، جراحی و..)
  - حداکثر ظرف ۷ روز توسط مجری به اسپانسر و کمیته اخلاق (به طریق مقتضی)
  - ۱۵ روز تقویمی توسط اسپانسر به اداره کل دارو در قالب فرم CIOMS

- Council for International Organizations of Medical Sciences (CIOMS)



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Progress Reports

- The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.
- The investigator should promptly provide written reports to the sponsor, the IRB/IEC and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

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بررسی گزارش مطالعات بالینی

- گزارش/گزارشات بینابینی و پایانی مطالعات بالینی بایستی پس از تایید مجری و همکاران و اعضای کمیته DSMB بر اساس راهنمای ICH3 و راهنمای تدوین گزارش مطالعات بالینی اداره کل توسط اسپانسر جهت بررسی و اعلام نظر به اداره کل دارو ارائه گردد.

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Premature Termination or Suspension of a Trial

- If the trial is prematurely terminated or suspended for any reason, the investigator/institution
  - should promptly inform the trial subjects,
  - should assure appropriate therapy and follow-up for the subjects
  - where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies).

- If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator
  - Should promptly inform the sponsor and the IRB/IEC
  - Should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

Final Report(s) by Investigator

- Upon completion of the trial, the investigator, where applicable, should
  - Inform the institution;
  - Should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

Section 4.0 Investigator Responsibilities

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Summary

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Monitoring and Auditing

- The study data that are generated must be of the highest quality; data must be accurate and evaluable in support of marketing clearance/ product approval and collected in a manner that protects the rights, safety and welfare of properly consented trial participants.

- Both monitoring and auditing can provide this oversight, albeit in different ways .

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Purpose

- The rights & well being of the human subjects are protected .
- The reported trial data are accurate ,complete and verifiable from source documents.
- To prevent, detect, correct and document:
  - Careless errors
  - Neglect
  - Fraud
  - Violations

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What is required?

- Professional qualifications / competence
- Training in GCP
- Thorough familiarity with:
  - Protocol
  - Investigational product
  - Study procedures
  - Informed consent form
  - CIP
  - Case report form
  - GCP and sponsor's SOP

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Types of Monitoring Visits

The most common types of site visits for industry-sponsored studies are:

- Site Assessment (Pre-Study) Visit
- Site activation , investigator meeting
- Site Initiation Visit
- Interim Monitoring Visit
- Close Out Site Visit

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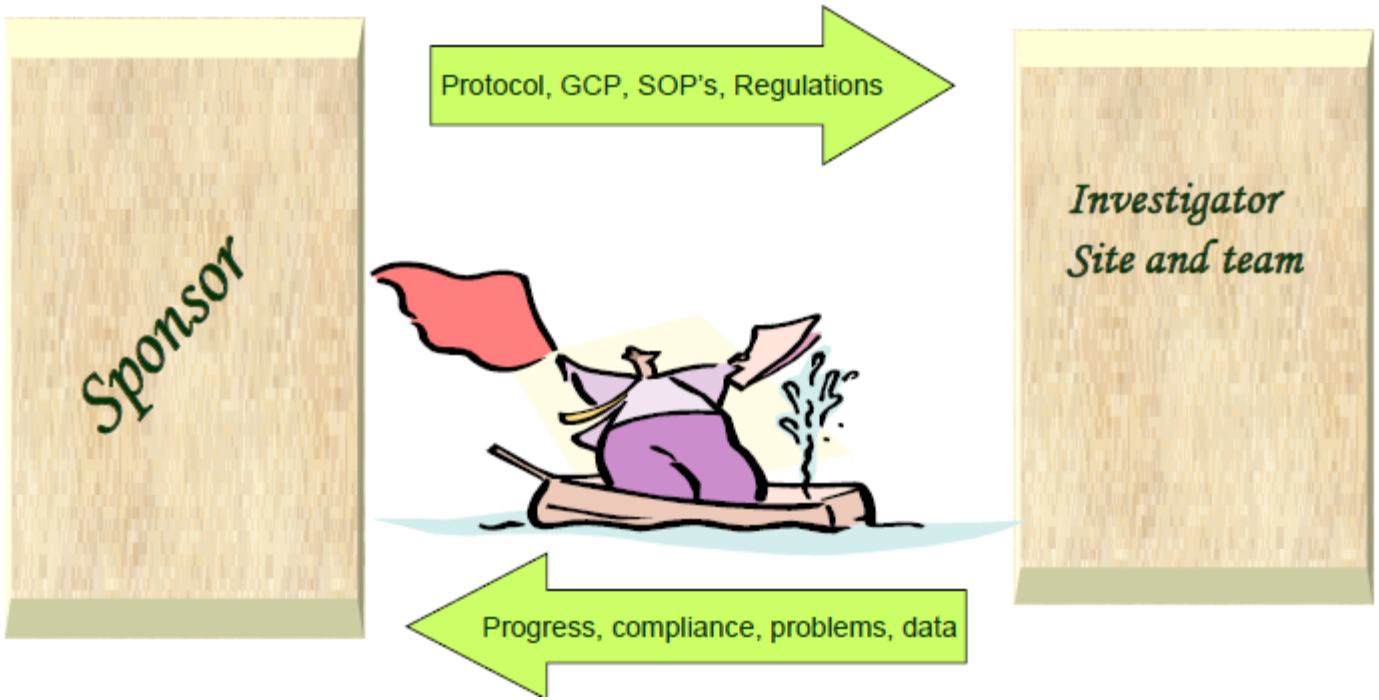
Monitor's Responsibilities

- Acting as the main line of communication between the sponsor and the investigator.



Monitor's Responsibilities

1- Verifying that

- Investigator has adequate qualifications and resources and remain adequate throughout the trial period

- Facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

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Monitor's Responsibilities

2- Verifying, for the investigational product

- Storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
- the investigational product(s) are supplied only to subjects who are eligible
- Subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
- The receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
- The disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

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Storage condition

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Monitor's Responsibilities

3- Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

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Monitor's Responsibilities

4- Verifying that written informed consent was obtained before each subject's participation in the trial.

Monitor's Responsibilities

5- Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

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Monitor's Responsibilities

6- Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

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Monitor's Responsibilities

7- Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

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Monitor's Responsibilities

8- Verifying that the investigator is enrolling only eligible subjects.

9- Reporting the subject recruitment rate.

10- Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

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Monitor's Responsibilities

11- Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

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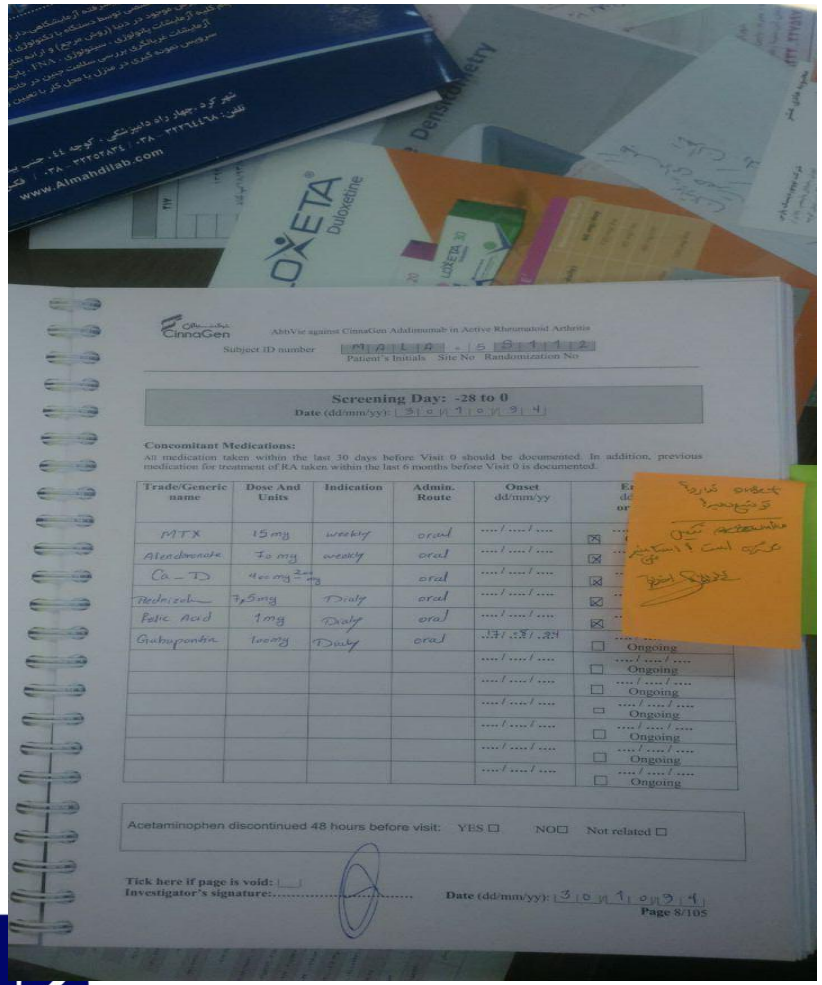
Monitor's Responsibilities

12- Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. Should verify that:

- The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
- Adverse events, concomitant medications are reported in accordance with the protocol on the CRFs.
- Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
- All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

CRF, source documents



Monitor's Responsibilities

13- Informing the investigator of any CRF entry error, omission, or illegibility.

- The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator.
- This authorization should be documented.

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Monitor's Responsibilities

14- Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

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Monitor's Responsibilities

15- Determining whether the investigator is maintaining the essential documents

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Monitor's Responsibilities

16- Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

Monitoring Report

- The monitor should submit a written report to the sponsor-investigator after each clinical monitoring activity.
  - Reports should include the date, site, name of the monitor, and name of the sponsor investigator or other individual(s) contacted.
  - Reports should include a summary of what the monitor reviewed and the monitor‘s statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.
- The review and follow-up of the monitoring report by the sponsor-investigator should be documented

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Auditing

- Auditing, a quality assurance function, is an independent, top-down, systematic evaluation of trial processes and quality control

Monitoring vs. Audit (1)

	Monitoring	Audit
Position	Part of trial conduct	Independent, third party
Focus	Trial conduct	Trial compliance
Timing	Trial duration	One time point – snapshot in time
Approach	Surveillance/ partnering	Systematic
Interfaces	Sponsor and site	Regulatory authorities

Differences between Auditing versus Monitoring:

Auditing Function

Monitoring Function

It turns out you can see both the forest AND the trees if you utilize each compliance function!

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Audit vs. Inspection

	Audit	Inspection
Who conducts them?	Independent unit of sponsor company	Regulatory authorities, IRB/IEC, data protection agencies
What do they check?	Trial conduct and compliance with: • Protocol • ICH-GCP • Regulatory requirements	
When do they occur?	Any time before, during or after the trial	
Why do they occur?	Randomly 'For-cause'	
How can you help/prepare?	Follow the protocol Document and file everything	

Thank You!

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