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# PART 1 | IMAGING IN CLINICAL PRACTICE

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A 40 year-old female presented with cough of 10 days duration. She described attacks of orthopnoea with gastric discomfort and heart burn. Clinical examination revealed nothing of significance.
The followings are the PA view of chest XR ( Figure 1) and a CT scan of the chest (figure 2).

**Q1: Describe the CXR findings?**
**Q2: What are the differential Diagnosis?**
**Q3: What is the diagnosis?**

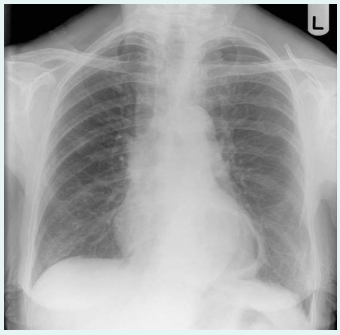

**Figure 1:** Chest X ray, PA view

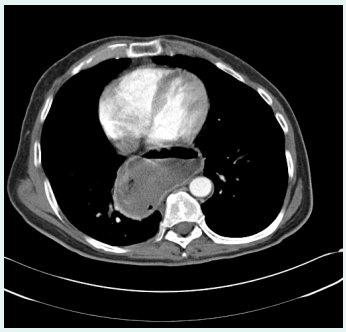

**Figure 2:** CT scan of the chest with IV contrast ( mediastinal window ) axial section.

## ANSWER OF Q1:

**Findings on chest X-Ray** (Figure 1 ): Chest X ray shows a well defined cystic lesion behind the heart on the left side with fluid level. (See the arrow in figure 3)

**Findings on CT scan** ( Figure 2): Shows a cystic lesion behind the heart with air fluid level continuous with oesophagus superiorly.

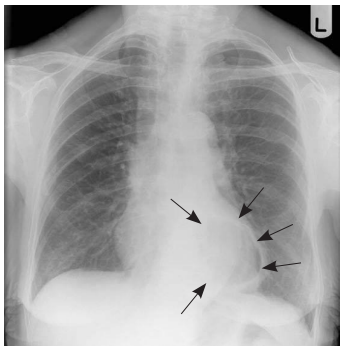

**Figure 3:** Black arrows on the margin of the cyst

## ANSWER OF Q2:

- Hiatus Hernia: appear as a retrocardiac cyst.
- Bochdalek hernia ( mostly posterior on the left side ) usually containing bowel, spleen or kidney).
- Morgagni hernia ( rare and usually right side and anterior ) can containing fat, omentum, liver and transverse colon.
- Lung Abscess in the posterior basal segment of the left lung, can be differentiated by presence of fever and symptoms of pneumonia.
- Bronchogenic cyst ( mediastinal type ).
- Enteric cyst ( sometimes referred as oesophageal duplication cyst ) usually in the posterior mediastinum.
- Neuroenteric cyst ( in the posterior mediastinum ) associated with vertebral anomalies.

## ANSWER OF Q3:

Diagnosis is ***hiatus hernia (HH), para-oesophageal type***.
HH is often asymptomatic but can produce dyspnea, retrosternal chest pain, epigastric discomfort and iron deficiency anaemia.
It appears as a round soft tissue mass often containing gas or air-fluid level behind the heart and usually lies to the left of the midline in the posterior mediastinum.
The larger hernias can also contain small intestine, colon and liver.
The diagnosis is readily confirmed by lateral film or barium meal and can also be confirmed by CT scan.

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# Clinical trials: what should we know about them?

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Clinical trial is a scientific experimental study to compare the effect and safety of an intervention against a control in human being. It is the best tool to provide high quality of evidence among other study designs.

## INTRODUCTION

Clinical trial is a scientific experimental research study comparing the effect and value of intervention against a control in human being.[1, 2] The intervention may be devices, drugs, or procedures; also it can be diagnostic, prophylactic or therapeutic.[3] The type of control can be (1) placebo, (2) no treatment, (3) different dose or regimen of the trial test treatment, control(s).[4] Or (4) the standard treatment.

Nowadays, new drugs, therapies and devices are consistently produced. In order to verify their effectiveness and safety in clinical practice, they should be enrolled in scientific studies.[5] The importance of clinical trials arises from its effect on patient management.[6,7] Nowadays, we are living in era of evidence based medicine, [8] medical research is the corner stone in building up evidence by providing a scientific data to allow clinicians to decide which best is suitable for their patients.[9]

Randomized Controlled clinical trials provide the strongest available, unfiltered knowledge to aid doctors in their decisions to treat their patients.[10, 11] (See figure 1)

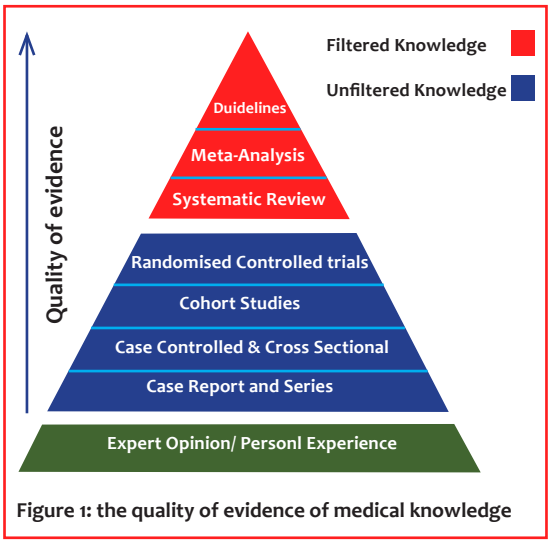


**Figure 1: the quality of evidence of medical knowledge**

## History of clinical trials

The first clinical trial was done by the Babylonian leader King Nebuchadnezzar II.[12] Ibn Sina (Avicenna) in 10th century had mention in his book Al- Quanun fi al-Tibb (the law in Medicine) the recommendation of testing new drugs on animals and human and sat down 7 basic rules for clinical drug trials.[13, 14]

In 1747, James Lind (1716–1794) used a control group on treatment of scurvy for the first time in a clinical trial by using lemons and orange.

The concept of comparing placebo with active treatment was first introduced in 1863 by Austin Flint (1812-1886).

In 1948; The British Medical Research Council introduced the first proper randomized clinical trial on the effect of streptomycin on tuberculosis though others think that it was proceeded by the trial of J. Burns Amberson on tuberculosis in 1926 ( published in 1931).

## What do you need to conduct clinical trials?

Before a clinical trial begins, a clear and well designed protocol should be prepared based on scientific methods to answer specific research questions. This protocol should be ethically approved by an independent ethics committee or institutional authority to secure health of the participants, then it should be registered.[15, 16, 17]

The concept and the content of a protocol vary according to the guideline it follows. In

general a protocol describes what types of people may participate in the trial, the schedule of tests, procedures, medications, dosages, and length of the study; it is the plan on which a clinical trial is based.[18]

According to the Guidelines of Good Clinical Practice (GCP) for development of a protocol of a clinical trial, we list down the recommended items to address in designing a Clinical Trial Protocol. "Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

* Study Summary:

Study summary should include the following:

- Protocol title
- Study phase
- Duration of the study
- Methodology
- Study site
- Approximate number of subjects
- Name, title, address, and telephone number of the PI, Co-PI, sponsors and study coordinators
- Investigator's affiliation

* List of Abbreviations
* Background Information/Significance
* Objectives/Rationale/Research Question
* Clinical Study Design
* Inclusion and Exclusion criteria of the Subjects
* Informed consent form process
* Adverse Event Reporting
* Assessment of Safety and Efficacy
* Treatment of Subjects
* Data Collection Plan
* Data Access
*Publication and Presentation Plans
* Timeline
* References

## Challenges of clinical trials

1. Study design type e.g double blind since open-label approach may bias patient and physician response and behaviour. This can be overcome by randomization, the process by which each subject has the same chance of being assigned to either intervention or control and it reduced selection bias, also blinding will reduce performance bias and investigator bias it is either:

**Figure 2: On the left James Lind (1716-1794); On the right Austin Flint (1812-1886)**

***Single blind trial***: Here the participant is not aware whether he belongs to the study or control group.

***Double blind trial***: Here one researcher allocates a series of numbers to 'new treatment' or 'old treatment'. The second researcher is told the numbers, but not what they have been allocated to.

***Triple-blind trial***: Here the participant, the investigator and the person analyzing the data are all blind. This is the ideal but double-blinding is the most commonly used.[16]

2. Difficulty in accessing the appropriate patient population, slow patient recruitment rate, and patient drop-out
3. Time: it takes long time to recruit enough participants and keeping them for long period.
4. Cost: which include cost involved in research participation, Difficulty in obtaining funding, and excessive trial cost not covered by trial sponsor.
5. Problem in obtaining informed consent.

Every clinical trial in the United States must be approved and monitored by an Institutional Review Board (IRB) to make sure the potential risks to participants are as low as possible. Every institution that conducts clinical trials has an IRB.[1] An IRB is a committee of health care professionals and community members that do not have connections to the specific clinical trial. The IRB committee allows for unbiased decisions to be made about the clinical trial and patient safety

Informed consent is the process of learning about the clinical trial before deciding to participate. Before someone can participate in a clinical trial they must review and sign an informed consent form.[18, 19]

The informed consent form should include the following information:

- Clinical trial process, including tests that may be conducted
- Known risks and benefits of experimental treatment
- Length of clinical trial
- Clinical trial contact information

## The journey of new drug or medicinal product

The journey of a new drug or medicinal product starts with pre-clinical research which includes laboratory or investigational studies on animal. Then after the pre-clinical research seems promising, an Investigational New Drug Application (IND) must be filled; it describes the results of pre-clinical studies and clearly defining how future studies will be conducted.

An investigational new drug application have to be reviewed and approved by independent committee e.g the US Food and Drug Administration (FDA) then it can proceeded into clinical trial. (Phase I)

## Phases of clinical trial

Development of new drug should pass through several steps "phases" of clinical trials.[19, 20] There are 4 phases; phase I and II are early stages, while phase III and IV are late stages.

***Phase I***: usually done on small group of healthy people, sometimes on patients to test drug safety.

***Phase II***: usually done on large group to evaluate drug safety and effectiveness. (Efficacy studies)

***Phase III***: to compare new intervention with standard of care or placebo (Large-Scale Testing)

***Phase IV***: to obtain large-scale, long term studies of morbidity and late effect (post marketing clinical trial) .

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**Single choice questions about this article are on the next page**

# Questions about Clinical trials

## Choose the most appropriate answer:

1. ***Clinical trial is a scientific experiment research study comparing the effect and value of intervention against control on:***
   - **(a)** Human.
   - **(b)** Animals.
   - **(c)** Human and animal.
   - **(d)** None of the above.

2. ***The control in clinical trial can be:***
   - **(a)** placebo.
   - **(b)** No treatment.
   - **(c)** The standard treatment.
   - **(d)** All of the above.

3. ***The importance of clinical trial arises from its effect on?***
   - **(a)** New drugs.
   - **(b)** New devices.
   - **(c)** New therapies.
   - **(d)** Patient management.

4. ***With the concept of "evidence – based medicine", randomized controlled clinical trial lies on the top of the:***
   - **(a)** Filtered clinical evidence.
   - **(b)** Unfiltered clinical evidence.

5. ***The first clinical trial was conducted by:***
   - **(a)** Babylonian king Nebuchadnezzar II.
   - **(b)** Ibn- Sina.
   - **(c)** James Lind.

6. ***To conduct a clinical trial we need:***
   - **(a)** A study protocol.
   - **(b)** The trial should be ethically approved.
   - **(c)** The clinical trial must be registered.
   - **(d)** All the above.

7. ***The concept and content of a protocol in the clinical trial is the same in all the protocol guidelines:***
   - **(a)** True.
   - **(b)** False.

8. ***Which of the challenges of clinical trials can be solve by randomization and blinding :***
   - **(c)** Study design type.
   - **(d)** Difficulty in accessing the appropriate patient population.
   - **(e)** Cost of the trial.

9. ***Ethical improvement in clinical trial is important because it:***
   - **(a)** Answers research question.
   - **(b)** Safeguards the health of participant.
   - **(c)** Prepares a study protocol.
   - **(d)** Finds out the cost of the trial.

10. ***The journey of new drug or medicinal product start with:***
    - **(a)** Pre-clinical research in lab rotary and animal studies.
    - **(b)** Phase I of clinical trial.
    - **(c)** An Investigational New Drug Application.

# Prevention of Diabetes Mellitus: what international guidelines tell us

**Editor-in-Cheif**

Diabetes Mellitus is a common disease. It is an incresing health problem in all communities especially in the middle east. Tretment of patient aiming at good control is the hope to prevent or delay the development of complications. The American Diabetic Association (ADA), in its quideline 2015 is trying to address the question; Is diabetes mellitus preventable? to know the answer please try to answer the following questions, correct answers are on page 58-59.

***1. Regarding screening for type 2 Diabetes Mellitus:***

**(a)** Screening should be started at age of 60 as DM is prevalent in those age groups.

**(b)** Doing fasting blood glucose level is enough for baseline screening.

**(c)** Presence of any risk factor for diabetes Mellitus mandates screening regardless of the age.

**(d)** Screening should be repeated every 3 years.

***2. The following are recognized risk factors for diabetes mellitus:***

**(a)** Polycystic ovary syndrome.

**(b)** Asthma.

**(c)** Obstructive sleep apnea.

**(d)** First degree relative with DM.

***3. Children and type II DM:***

**(a)** Type II DM does not occur during childhood.

**(b)** Overweight child with ≥ risk factor should be screen every 3 years for DM.

**(c)** Unlike in adult positive family history of DM is not a risk factor for the child to have type II DM.

**(d)** Gestational DM in women is considered a risk factor of DM for the child.

***4. Gestational DM:***

**(a)** It means high blood glucose level diagnosed in the first trimester.

**(b)** It needs no treatment as it has trivial effect on the pregnancy.

**(c)** Gestational diabetes is a risk factor for diabetes in the future.

**(d)** Gestational diabetes may lead to delivery of large weight baby.

***5. Screening of pregnant women for type II diabetes:***

**(a)** To detect the probability of a woman to have gestational diabetes, we should measure blood glucose level prenatally.

**(b)** Every pregnant woman who has no history of DM should be screened at 24 weeks of gestation to search for gestation DM.

**(c)** In the post partum period woman with gestation diabetes should be screened for persistent diabetes on the 7th day.

**(d)** If the blood glucose level returns to normal after delivery monitoring should be defer till the next pregnancy.

***6. Prediabetes:***

**(a)** *It is a potential risk to become true type II DM in the future.*

**(b)** *It only means that FPG is between 100 – 125 mg/dl.*

**(c)** *Those with prediabetes should be screened every year.*

**(d)** *HbA1c has no role in the diagnosis of prediabetes.*

***7. Progression of prediabetes:***

**(a)** Follow up without active intervention is the only what we can offer at this stage.

(b) Body weight loss of > 7 % should be targeted to delay or prevent diabetes.

(c) Use of Metformin can halt the progression of prediabetes to frank DM.

(d) Diet restriction is not of benefit at this stage.

***8. Use of drugs to treat prediabetes:***

(a) Metformin is the only drug approved to be used in prediabetec stage.

(b) Sulfonylurea is not recommended at this stage.

(c) Patients aged > 60 years or those with BMI < 25 are the best candidates for the positive effect of metformin.

(d) Treatment of modifiable CVD risk factors ( obesity, Hypertension, dyslipidemia) should be part of our plan to treat prediabetes

***9.Diagnostic criteria of frank Diabetes Mellitus:***

(a) Diagnosis of DM can be made if a patient has symptoms suggestive of DM in whom Random PG ≥ 200 mg/dl ( 11.1 mmol/l)

(b) HbA1c ≥ 6.5 % is enough for the diagnosis of DM regardless of the method of standardization used by the laboratory.

(c) Fasting in the term FPG is defined as no caloric intake for ≥ 6 hours.

(d) We may need 2 separated blood samples for the diagnosis of DM for the first time.

***10. Management of DM during pregnancy:***

(a) We should targeting HbA1c of < 7% before attempting conception..

(b) Statin can be used safely during pregnancy..

(c) During pregnancy the goal is achieve HBA1c of 7 %.

(d) Screening for retinopathy is not needed during pregnancy .

## The answer of Questions about clinical trials (Page 55)

1. ***The correct answer is (a)***:
   clinical trials are conducted on humans, basic researches are conducted on animals.
2. ***The correct answer is (d)***:
   All can be used in the control group.
3. ***The correct answer is (d)***:
   The overall importance of clinical trials is to improve management of patients.
4. ***The correct answer is (b)***:
   Clinical trials offer the best unfiltered evidence.
5. ***The correct answer is (a)***:
6. ***The correct answer is (d)***:
   all are essential to conduct a clinical trials.
7. ***The correct answer is (b)***:
   They vary according to the guidelines used.
8. ***The correct answer is (b)***:
9. ***The correct answer is (b)***:
10. ***The correct answer is (a)***:

# Prevention and delaying of Diabetes Mellitus: what international guidelines tell us

## Answers of Questions on page 46-47

1. ***Answers (F, F, T, T)***: ADA recommend to start screening of any adult at age of 45 years, especially if the person is overweight or obese ie BMI >= 25. Any adult person who has at least one risk factor for Diabetes Mellitus should be screened regardless the age. It is recommended to repeat the test every 3 years in those who show normal results on the first screen. Fasting blood glucose level is not enough to screen a person for diabetes mellitus. We should do 2hours postprandial blood glucose level, and HbA1c in addition to fasting blood glucose level.
2. ***Answers ( T, F, T, T)***: see table 1 for the risk factors for DM according to the ADA . (See **table 1**)
3. ***Answers ( F, T, F, T)***: Type II DM in increasingly diagnosed in Children. Child who is overweight and having ≥ risk factor for DM should be screen by HbA1c at 3 year intervals starting from age of 10 years. The risk factors for type II DM in children are family history of type II DM in first and second degree relative, certain ethnic groups like Native American, signs of insulin resistance, and maternal DM or gestational DM during child's gestation.
4. ***Answers (F, F, T, T)***: Recently gestational diabetes is limited to detection of high blood glucose level in the second and third trimester. High blood glucose level in the first trimester is diagnosed as type II diabetes Mellitus. As the case in type I and II DM, gestational diabetes has the same bad effect on the mother and the baby including delivery a high weight baby so it should be treated according the guidelines. History of gestational diabetes, even if it returns to normal after delivery is a risk factor for having frank type II diabetes in the future so it necessitate screening.
5. ***Answers ( F, T, F, F)***: in order to detect undiagnosed type II diabetes or prediabetes especially in women with risk of diabetes we should measure blood glucose level in the prenatal visit. In women who do not have DM, blood glucose level should be measured at 24-28 weeks of pregnancy to detect gestational diabetes mellitus. The best time to search for persistent gestational DM is 6-12 weeks after delivery. Gestational diabetes is a risk factor for having diabetes M in the future so every women with gestational DM should be screened on 3 year interval; however, if she is diagnosed as prediabetes then the screen should be every year.
6. ***Answers ( T, F, T, F)***: Prediabetes is a condition where blood glucose level falls short of the diagnostic criteria for frank type II DM, but not within the normal range. It includes fasting glucose intolerance, post prandial glucose intolerance and HbA1c of 5.7-6.4 %. Any one of the above is enough to diagnose prediabetes. The importance of prediabetes is that the potential transformation to frank diabetes Mellitus so person with prediabetes should be screened ever year rather than every 3 years as the case with normal blood glucose level with risk factors.
7. ***Answers ( F, T, T, F)***: Recommendation stated that we can delay or even prevent type II DM by providing some interventions at prediabe-

**Table 1: Diabetes risk factors**

| |
|---|
| Physical inactivity |
| First degree relative with diabetes |
| High risk race/ ethnicity |
| Women who delivered a baby > 9 lb or were diagnosed with gestational dm |
| HDL-C < 35 mg/dl ± TG >250 mg/dl |
| Hypertension ( ≥ 140/90 or on therapy) |
| A1c .= 5.7 %, IGT, or IFG on previous tests |
| Conditions associated with insulin resistance: severe obesity/ acanthosis nigricans/ PCOS |
| CVD history |

tes stage. The interventions that approved by the ADA to affect the progression are intensive diet and promoting physical activity that target achieving of body weight loss of >7 % and performing physical activity ≥ 150 min/ week of moderate activity. Metformin can be used for this purpose.

8. ***Answers ( T, T, F, T)***: ADA in its 2015 guidelines approved metformin only to be used for the treatment of prediabetes in addition to behavior counseling. Metformin is especially useful in the followings: BMI. 35 kg/M2, Age < 60 years, and women with prior gestational DM. ADA is suggesting screening for and treating of modifiable CVD risk factors like obesity, hypertension and dyslipidemia in any patient diagnosed with prediabetes.

9. ***Answers ( T, F, F, T)***: ADA recommended that we can diagnose DM by HbA1c, FPG, Random PG, or Oral GTT for the diagnosis of type II DM ( Table ). For HbA1c to be dependable for the diagnosis of DM, it should be performed in a laboratory using NGSP- certified method and standardized to DCCT assay. Otherwise the results are not dependable. For the blood sample to fulfill the requirement of being fasting, it should be withdrawn 8 hours after the last caloric intake. And for the sample to be random it should be withdrawn 2 hours after the last caloric intake. Unless clinical diagnosis of DM is clear, same test to be repeated immediately using a new blood sample for confirmation.

10. ***Answers (T, F, F, F)***: the recommendation is to have HBA1c < 7 % before attempting conception. Statin, ACI inhibitors, ARBs, and most non-insulin therapies are contraindicated or not recommended during pregnancy. The target during pregnancy is to have HbA1c 6 % with the least risk for hypoglycemia. Women with pregestational diabetes should underwent baseline ophthalmologic examination in the first trimester then once in each trimester during the whole pregnancy.

***The questions and answers are based totally on the quidelines of the American Diabetic Association 2015.***

***American Diabetes Association. Standards of medical care in diabetes—2015. Diabetes Care. 2015;38(suppl 1):S1-S93.***