**Verification of therapeutic safety - Clinical trial**

**Aim of this practical activity:**

* acquiring the skills needed to conduct therapeutic safety evaluation studies

**Utility:**

* **conducting studies to verify therapeutic safety for the thesis, personal research.**
* **understanding and interpreting the therapeutic safety studies that you will read as future clinicians**

**Scenario**

The scenario below is built after the study presented in the article:

Inagaki N, Harashima S, Maruyama N, Kawaguchi Y, Goda M, Iijima H. ​​Efficacy and safety of canagliflozin in combination with insulin: a double-blind, randomized, placebo-controlled study in Japanese patients with type 2 diabetes mellitus. Cardiovasc Diabetol. 2016 Jun 18; 15: 89Scenariul de mai jos este construit după studiul prezentat în articolul:

Available at:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4912792/>

details about the study Clinical Trial.gov [NCT02220920](https://clinicaltrials.gov/ct2/show/NCT02220920?rslt=With&type=Intr&cond=%22Glucose+Metabolism+Disorders%22&phase=3&draw=2&rank=11)

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| „A randomized, parallel, triple-blind (participant, physician, evaluator) multicenter trial was conducted to assess the efficacy and safety of canagliflozin in Japanese patients with T2DM. Eligible patients were randomized to placebo (PLA) or 100 mg canagliflozine (CF) once daily before breakfast for 16 weeks. Randomization was performed using a block allocation method (1: 1, blocks of 4 in total 87 blocks).  The study was approved by the Ethics Committee in each center. All patients gave their consent in writing.  Adults with type 2 diabetes (T2DM) with stable diet and physical activity who received a stable dose and treatment (insulin) for 12 weeks before treatment and glycemic hemoglobin levels (HbA1c) between ≥ 7.5 and <10.5%. Patients were excluded with:  severe diabetic complications; systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg; severe kidney or liver disease; alcoholics; pregnant women.  The primary endpoint was the change in HbA1c levels. The secondary endpoint was safety assessment based on adverse events and hypoglycaemic events.  "Adverse events were understood to be adverse events by the investigator. Hypoglycaemia was considered to be either low glycemia without symptoms (≤70 mg / dl) or hypoglycaemic episodes with typical hypoglycaemic symptoms, regardless of blood glucose level.  One patient in the CF group was mis-administered with placebo. This patient was included in the CF group in the analysis of efficacy and in the PLA group in the safety analysis (safety analysis set). |

**Research protocol**

**1.** **Aim, objectives and hypothesis of research (fill in the spaces below)**

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| **Definitions:** (fill in the MeSH medical dictionary with the following definitions)   * **Diabetes Mellitus, Type 2** * **Canagliflozin**   **Aim** (based on the scenario, fill in the aim of this study):      **Objectives** (does not require filling)   * **Objective 1**. Studying the comparability of the studied samples:   o Is there a statistically significant difference between HbA1c averages in patients who received CF versus those who received PLA?   * **Objective 2**. Studying the risk of adverse events arising from CF treatment:   o Is there a statistically significant difference between the frequency of adverse events in patients receiving CF versus those who received PLA?   * **Objective 3**. Quantifying the magnitude of the risk of adverse events arising from CF treatment.   + Using the indicators: relative risk (RR), absolute risk reduction (ARR), the number needed to cause physical harm (NNHF) * **Objective 4**. Study of the risk of hypoglycaemic episodes following treatment with CF:   + Is there a statistically significant difference between the frequency of episodes of hypoglycaemia in patients receiving CF versus those who received PLA? * **Objective 5.** Quantifying the magnitude of the risk of hypoglycaemic episodes following treatment with CF:   + Using indicators: relative risk (RR), absolute risk reduction (ARR), the number needed to cause physical harm (NNHF) |

**2. Domain of research** (fill in the blanks)**:**

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**3.Study type:**

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| A. Based on study objectives (fill in): |
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| B. Based on the results (fill in): |
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| C. Using matching technique (fill in): |
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| D. Depending on design (fill in): |
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| E. Depending on the drug development phase (fill in): |

**The methods used to ensure the validity of the study**

* Did the subjects have been assigned to random treatments? (YES / Unclear / NO)
* Was it stated if the allocation was concealed ("allocation concealed")? (YES / Unclear / NO)
* Have all patients been analyzed in the appropriate group for what they were given? (analysis was of the "safety analysis set" type?) ")? (YES / Unclear / NO)
* Was the double blind method used? (YES / Unclear / NO)
* Was the trial controlled? (YES / Unclear / NO)

**4.** **Target population and study sample (fill in the spaces below)**

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| **Target population**   * Clinical features (fill in): * Demographics (fill in): |
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| **Accessible population**(fill in): |
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| **Inclusion and exclusion criteria:**  • **Inclusion criteria:**  Clinical characteristics:  Demographic characteristics:  •**Exclusion criteria** (applied only to subjects who comply with the above inclusion criteria; if not relevant, some or all exclusion criteria may be missing):   * Biasing factors (e.g. coexistent diseases/coexistent treatments): * Adverse effects: * Factors that make data collection difficult or impossible: * Ethic issues: |
| **Was the sample size calculated? (YES / Unclear / NO)** |

**5. Data collection method**

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| A. Based on the studied population(fill in): |
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| Write the sampling method (fill in): |

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| B. Based on the duration of data collection(fill in): | | |
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| C. Based on the technique used in the choice of groups(fill in): | | |
|  |  | Write the outcome (**outcome**): |
|  |  | Write the exposure factor **(exposure)**: |
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**6. Defining variables.**

Database used**: file B\_AE.xls.**

**Ctrl click on the link to the database and save it to your account.**

Fill in the table, if necessary add extra lines.

|  |  |
| --- | --- |
| **Name of variable** | **Type of variable** |
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**7. Statistical analysis**

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| **Programs used for data processing (fill in):** |
| Methods (tests, indicators) used for data analysis   * Objective 1: * Objective 2: * Objective 3: * Objective 4: * Objective 5: |
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**Results: Data analysis**

**9. Analytical results (insert the results below). Interpretation for data analysis are also listed below in the Interpretation files.**

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| * **Objective 1.**   **Studying the comparability of the samples:**   * Is there a significant difference between the average of baseline HbA1c in patients who were subsequently treated with CF versus those who subsequently received PLA?   Table I. Initial HbA1c status in diabetic patients followed by the two intervention groups   |  |  |  |  | | --- | --- | --- | --- | | Characteristics of the subjects | Canagliflozin (n=154) | Placebo (n=138) | p | | **HbA1c (%)** |  |  |  |   ?Submitted (fill in):  n –number of subjects   * **Objective 2.**   **Studying the risk of adverse events arising from CF treatment:**   * Is there a statistically significant difference between the frequency of adverse events in patients receiving CF versus those who received PLA?   Table II. The observed contingency table (frequency distribution of patients with adverse events on the two intervention groups)   |  |  |  |  | | --- | --- | --- | --- | | **Group** | Nr. patients who had adverse events | Nr. patients who had no adverse events | **Total** | | Canagliflozin |  |  |  | | Placebo |  |  |  | | Total |  |  |  |   Fill in with the result of the test p=   * **Objective 3.**   **Indicators quantifying the magnitude of the risk of adverse events occurring with the new drug compared to placebo** (! Calculated if adverse reaction risk has been demonstrated)  RR=  ARR (RAR) =  NNH (NNVF) =   * **Objective 4.**   **Study of the risk of hypoglycaemic episodes following treatment with CF :**   * o Is there a statistically significant difference between the frequency of episodes of hypoglycaemia in patients receiving CF versus those who received PLA?     Table II. The observed contingency table (distribution of the frequency of patients with hypoglycaemic episodes in the two intervention groups)   |  |  |  |  | | --- | --- | --- | --- | | **Group** | Nr. patients who had episodes of hypoglycaemia | Nr. patients who did not have episodes of hypoglycaemia | **Total** | | Canagliflozin |  |  |  | | Placebo |  |  |  | | Total |  |  |  |   Fill in with the result of the test p=   * **Objective 5.**   **Indicators that quantify the magnitude of the risk of hypoglycaemic episodes following treatment with the new drug compared to placebo (**!Calculated if the risk of hypoglycaemic episodes has been demonstrated)  RR=  ARR (RAR) =  NNH (NNVF) = |

**Interpretation**

**10.** **Interpret the results.** Instructions (examples) for interpreting the results are available in the Interpretations file.

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| **Statistically:** | **•Objective 1. Studying the comparability of the samples:**  Is there a significant difference between the average of baseline HbA1c in patients who were subsequently treated with CF versus those who subsequently received PLA?   * YES/ NO * Motivating the choice:   **Conclusion: Were the samples comparable before the study? (answer): YES / NO**  **• Objective 2. Studying the risk of adverse events arising from CF treatment:**  Is there a statistically significant difference between the frequency of adverse events in patients receiving CF versus those who received PLA?   * YES/ NO * Motivating the choice:   **Conclusion:** CF treatment has a risk of adverse events from a statistical point a view? **(Answer):** YES/NO  **•Objective 3. Indicators quantifying the magnitude of the risk of adverse events occurring with the new drug .**   * + **RR**   + **ARR**   + **NNH**   **•Objective 4. Study of the risk of hypoglycaemic episodes following treatment with CF :**  Is there a statistically significant difference between the frequency of episodes of hypoglycaemia in patients receiving CF versus those who received PLA?   * YES/ NO * Motivating the choice:   **Conclusion: The CF treatment has the potential to produce hypoglycemia episodes from a statistical point of view?**  **(answer):** YES / NO  **•Objective 5. Quantifying the magnitude of the risk of hypoglycaemic episodes due to CF treatment.**  Interpretation:   * + **RR**   + **ARR**   + **NNT** |
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| **Clinic:** | **Appreciate the risk of developing hypoglycemic episodes in a clinical setting**   * Evaluate clinically the relative risk (in answer note that you have read in another study about a risk between another treatment and placebo and placebo of 2)   + RR: * Appreciate clinically the punctual estimator (in answer note that you have read other studies on hypoglycaemic episodes that considered clinically important 7% differences):   + **ARR:** * A single, randomized controlled trial of a small number of subjects, representative of the target population, without errors, showing a difference between the safety outcome of the treatments, is a good argument for causality (the treatment and not others factors have caused the occurrence of adverse events)? YES/NO |
| **Requirement:** Because this study has caught your curiosity, you want to read more on the same subject. Search in PubMed with Mesh:   * A review / last published study / last review published on the same topic * Indicate the Vancouver-style bibliographic reference found | |

**Laboratory Conclusions: Today's work helps you**

**• to carry out therapeutic studies or to test differences between quantitative groups of continuous data for the thesis or for other scientific papers**

**• to understand and interpret therapeutic studies and / or to use statistical tests that you read as cliniciansConcluziile**