11th Balkan Congress of Nuclear Medicine
May 30 to June 02, 2024
Skopje

FEASIBILITY STUDY - A MEAN FOR MULTI-FACETED ASSESSMENT OF THE IDEA OF ESTABLISHING RADIOISOTOPE PRODUCTION AND INTRODUCING NEW RADIOPHARMACEUTICALS INTO CLINICAL PRACTICE

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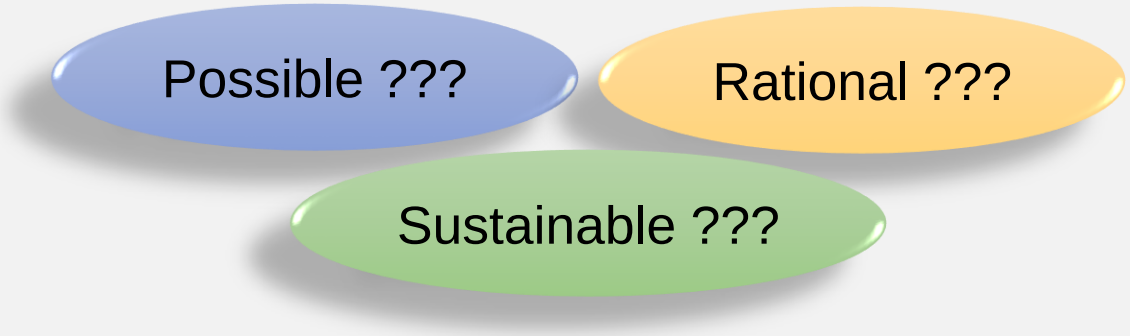
Establishing radiopharmaceutical production in a developing country is challenging, mainly in the economical aspect.



A feasibility study provides an objective insight into many aspects of the feasibility of the idea of introducing new radiopharmaceutical.

North Macedonia

- **Developing country in Southeastern Europe**
- **Centralized production – 1 facility for the production of PET radioisotopes and radiopharmaceuticals (University Institute of PET)**

Feasibility study for the establishment of production of zirconium-89 radioisotope and implementation of ^{89}Zr-radiopharmaceuticals in clinical practice

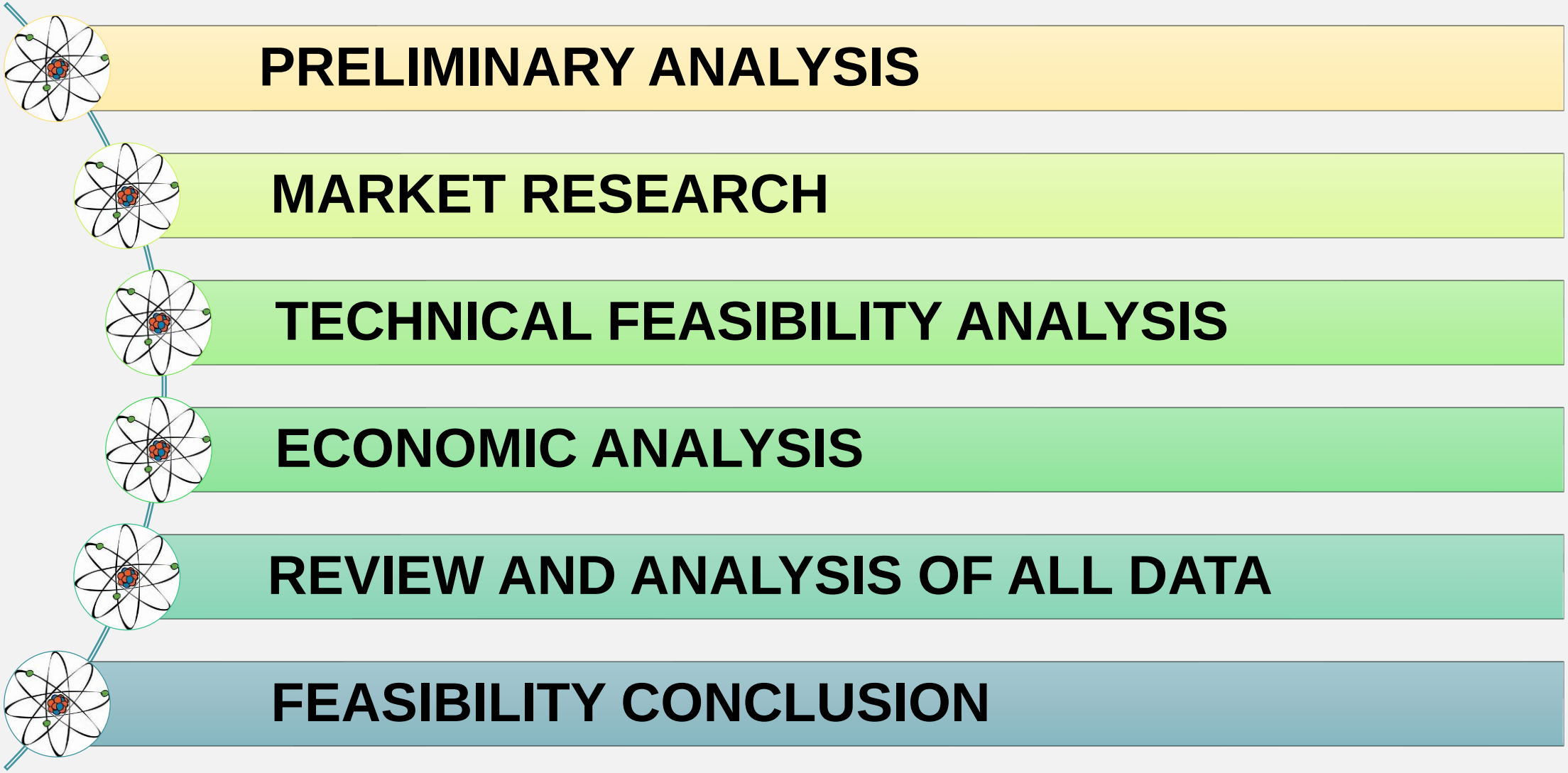
ZIRCONIUM-89

– EMERGING PET RADIOMETAL

Zirconium-89 half-life of 78.4 h corresponds to the biological half-life of monoclonal antibodies.

- **Half-life 78.4 h**
- **Immuno-PET radionuclide**
- **Labelling of antibodies, nanoparticles, proteins, peptides, and cells**

DESIGN OF FEASIBILITY STUDY



PRELIMINARY ANALYSIS

Objective: To assess whether the clinical application of ^{89}Zr-radiopharmaceuticals in the country is possible and justified.

Review of clinical applications data of ^{89}Zr-radiopharmaceuticals

- Reference database for clinical trials (ClinicalTrials.gov)

Review of statistical data regarding malignant diseases in North Macedonia: frequency, mortality, sex distribution, comparative analysis (EU, Southern Europe, world)

- Reference databases: international (Global Cancer Observatory) and domestic (Mortality Register and Cancer Register of Institute of Public Health)

PRELIMINARY ANALYSIS

Review of clinical applications data of ^{89}Zr-radiopharmaceuticals

- **Clinical trials in total** (until 09.05.2021): 93
- **Status - completed, terminated, unknown**: 48
- **Countries**: Netherlands – 28, USA – 16, Belgium – 2, China – 2, Australia – 1, Sweden – 1, Denmark – 1, Korea – 1, France – 1, Spain – 1
- **Radiopharmaceuticals**: ^{89}Zr-bevacizumab (**9**), ^{89}Zr-trastuzumab (**6**), ^{89}Zr-Df-IAB2M (**3**), ^{89}Zr- Cetuximab (**3**), ^{89}Zr-Pembrolizumab (**2**), ^{89}Zr-J591 (**2**), ^{89}Zr-panitumumab (**2**), ^{89}Zr-Girentuximab (**2**), ^{89}Zr-DFO-pertuzumab (**2**), ^{89}Zr-Df-IAB22M2C, ^{89}Zr-KN035, ^{89}Zr-MMOT0530A, ^{89}Zr-AMG211, ^{89}Zr-ABT806, ^{89}Zr-daratumumab, ^{89}Zr-Cripec Docetaxel, ^{89}Zr-GC1008, ^{89}Zr-durvalumab, ^{89}Zr-GSK3128349, ^{89}Zr-GSK2849330, ^{89}Zr-BI 754111, ^{89}Zr-GSK2398852, ^{89}Zr-RO5429083, ^{89}Zr-TAK-164, ^{89}Zr-nanocoll, ^{89}Zr-DS-8895a, ^{89}Zr-RO5479599

PRELIMINARY ANALYSIS

Review of cancer statistics

Neoplasms (C00-D48) are the ***second leading cause of death*** in Macedonia, after circulatory system diseases.

Deaths in 2020 due to malignant diseases	
1 – 64 years	> 64 years
24.25 %	12.68 %

Mortality Register, Institute of Public Health, 2021

2011-2020
The most common cause of death from malignant neoplasms:

average mortality rate in both sexes
180 per 100,000 population

Males: **bronchi and lungs cancer**
average mortality rate 63.9 per 100,000 men

Females: **breast cancer**
average mortality rate 29.07 per 100,000 women

Cancer Register, Institute of Public Health, 2021

PRELIMINARY ANALYSIS

Review of cancer statistics

10 most common primary cancer sites (N.Macedonia), 2011 - 2020

Total			Males			Females		
Code	Primary sites	%	Code	Primary sites	%	Code	Primary sites	%
C34	Bronchus and lung	13.12	C34	Bronchus and lung	18.80	C50	Breast	25.29
C50	Breast	11.59	C61	Prostate	9.77	C44	Other of skin	7.38
C44	Other of skin	8.22	C44	Other of skin	8.90	C54	Corpus uteri	7.30
C18	Colon	6.10	C16	Stomach	7.50	C34	Bronchus and lung	6.16
C16	Stomach	6.06	C18	Colon	6.50	C18	Colon	5.61
C61	Prostate	5.38	C67	Bladder	5.67	C53	Cervix uteri	5.16
C22	Liver and intrahepatic bile ducts	4.20	C22	Liver and intrahepatic bile ducts	5.08	C16	Stomach	4.30
C20	Rectum	4.00	C20	Rectum	4.38	C56	Ovary	3.83
C67	Bladder	3.93	C32	Larynx	3.85	C20	Rectum	3.53
C54	Corpus uteri	3.28	C25	Pancreas	3.10	C22	Liver and intrahepatic bile ducts	3.11
	Other	34.13		Other	26.44		Other	28.33

Cancer Register, Institute of Public Health, 2021

PRELIMINARY ANALYSIS

Review of cancer statistics

New cancer cases in 2020, excluding non-melanoma skin cancer, both sexes

World		EU-27		Southern Europe		North Macedonia	
Cancer	*%*	*Cancer*	*%*	*Cancer*	*%*	*Cancer*	*%*
Breast	11.7	Breast	12.1	Breast	12.6	Lung	14.9
Lung	11.4	Prostate	11.4	Lung	11	Breast	12.9
Prostate	7.3	Lung	10.8	Prostate	10.3	Prostate	10.3
Colon	6	Colon	7.4	Colon	8.6	Rectum	6.7
Stomach	5.6	Bladder	5.3	Bladder	6.5	Colon	5.6
Liver	4.7	Rectum	3.9	Rectum	4.1	Corpus uteri	4.8
Rectum	3.8	Melanoma of skin	3.6	Pancreas	3.2	Bladder	4.8
Cervix uteri	3.1	Pancreas	3.2	Stomach	3.2	Stomach	4.3
Oesophagus	3.1	Kidney	2.9	Non-Hodgkin lymphoma	3	Brain, central nervous system	4
Thyroid	3	Non-Hodgkin lymphoma	2.9	Kidney	2.9	Pancreas	3.6

Global Cancer Observatory, 2021

PRELIMINARY ANALYSIS

Review of cancer statistics

Top 5 most frequent cancers among new cases in females in 2020, excl. non-melanoma skin cancer

World		EU-27		Southern Europe		North Macedonia	
Cancer	*%*	*Cancer*	*%*	*Cancer*	*%*	*Cancer*	*%*
Breast	24.5	Breast	26.4	Breast	28	Breast	29.2
Colorectum	9.4	Colorectum	11.2	Colorectum	12.2	Colorectum	14.4
Lung	8.4	Lung	8.4	Lung	7.1	Corpus uteri	10.9
Cervix uteri	6.5	Corpus uteri	5.4	Corpus uteri	5.6	Lung	7.2
Thyroid	4.9	Melanoma of skin	3.8	Thyroid	3.9	Cervix uteri	3.3

Top 5 most frequent cancers among new cases in males in 2020, excl. non-melanoma skin cancer

World		EU-27		Southern Europe		North Macedonia	
Cancer	*%*	*Cancer*	*%*	*Cancer*	*%*	*Cancer*	*%*
Lung	14.3	Prostate	20.9	Prostate	18.8	Lung	21
Prostate	14.1	Lung	12.8	Lung	14.1	Prostate	18.5
Colorectum	10.6	Colorectum	11.9	Colorectum	13.6	Colorectum	10.9
Stomach	7.1	Bladder	7.6	Bladder	9.3	Bladder	7
Liver	6.3	Melanoma of skin	3.5	Stomach	3.6	Stomach	5.2

Global Cancer Observatory, 2021

PRELIMINARY ANALYSIS

Review of cancer statistics

Mortality (deaths of cancer in 2020), both sexes

World		EU-27		Southern Europe		North Macedonia	
Cancer	*%*	*Cancer*	*%*	*Cancer*	*%*	*Cancer*	*%*
Lung	18	Lung	20.3	Lung	20.2	Lung	23.3
Liver	8.3	Colon	8.5	Colon	9.5	Breast	7.5
Stomach	7.7	Breast	7.2	Breast	6.8	Prostate	7.1
Breast	6.9	Pancreas	7	Pancreas	6.7	Stomach	6.6
Colon	5.8	Prostate	5.5	Stomach	5.1	Pancreas	6.4
Oesophagus	5.5	Liver	4.2	Liver	5	Colon	6
Pancreas	4.7	Stomach	4.1	Prostate	4.8	Brain, central nervous system	6
Prostate	3.8	Bladder	3.9	Bladder	4.2	Rectum	5.8
Cervix uteri	3.4	Rectum	3.6	Rectum	3.4	Liver	4.4
Rectum	3.4	Leukaemia	3.4	Leukaemia	3.4	Bladder	3.1

Global Cancer Observatory, 2021

MARKET RESEARCH

Objective: To define the geographical impact of the market.

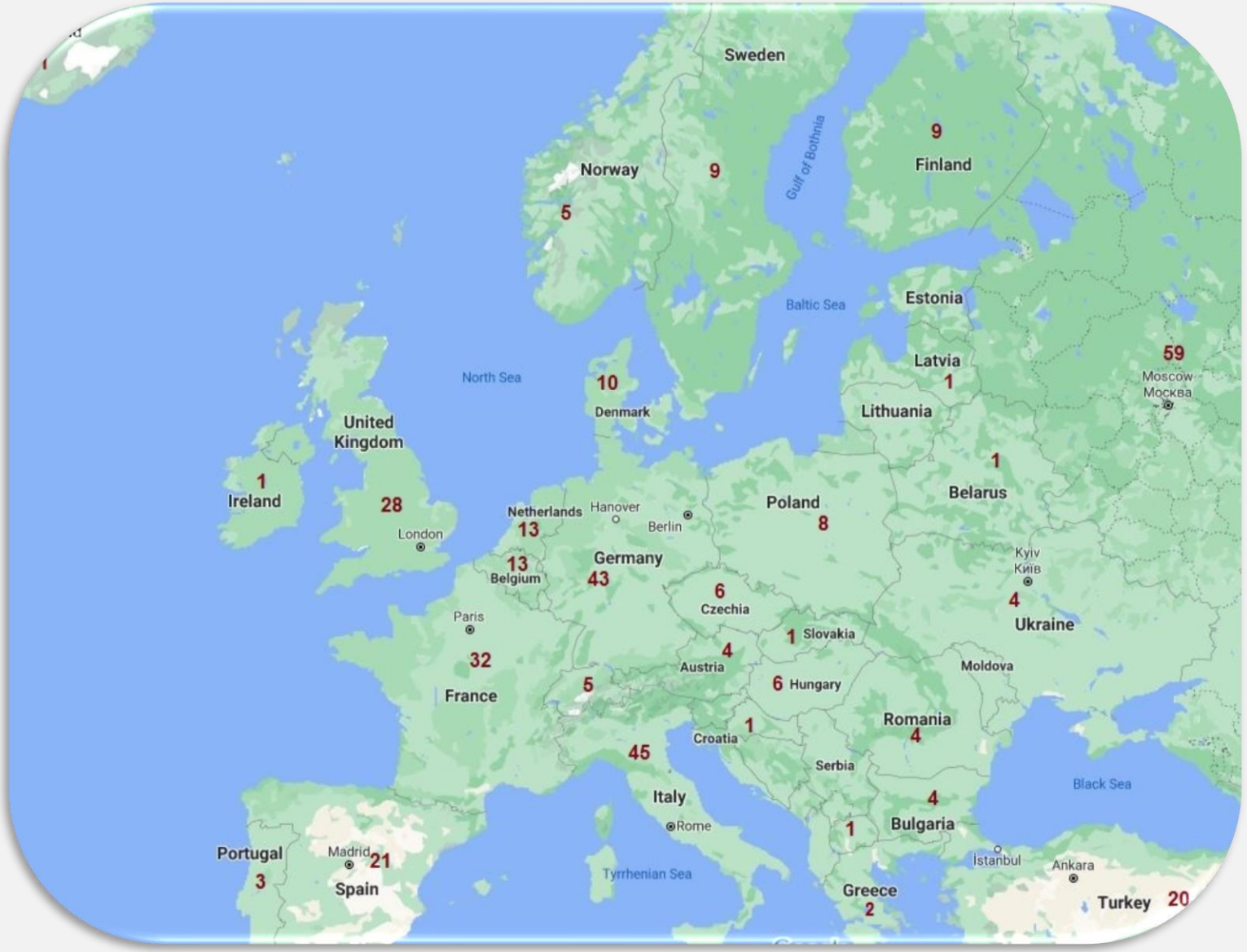
Distribution of medical cyclotrons in Europe

IAEA Cyclotron Distribution Database

Zirconium-89 production sites in Europe

Literature search

MARKET RESEARCH



Distribution of medical cyclotrons in Europe

Worldwide:
1266

Europe + Turkey + Russian Federation (including its Asian part):
356

https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx (December 2022)

MARKET RESEARCH

Zirconium-89 production sites in Europe

Netherlands (GMP compliant production of ^{89}Zr for the research community)

France

Turkey

Romania

United Kingdom

Germany

Italy

Russia

Belgium

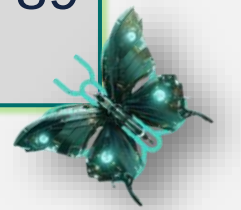
Portugal

Poland

No zirconium-89 production on the Balkan Peninsula

TECHNICAL FEASIBILITY ANALYSIS

Analysis of the ***technical capacities*** of the production site (University Institute of Positron Emission Tomography) in terms of *space* and *equipment* necessary for the realisation of the production of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals.



Objective: To determine what type of additional equipment/apparatus is required.

TECHNICAL FEASIBILITY ANALYSIS

Zirconium-89 radioisotope

Production mode: cyclotron | **$^{89}Y(p,n)^{89}Zr$**

UI PET technical capacities: → 3 production and 2 QC laboratories

Cyclotron PETtrace 860
- Beam energy 16.5 MeV
- Maximum current 100 uA on dual beam
- Targets for the production of ^{18}F, ^{11}C and ^{13}N radioisotopes and possibility for the additional embedding of solid targets

ECONOMIC ANALYSIS

Financial analysis

Cost analysis

Objective:

- ✓ To calculate the cost of in-house production of zirconium-89 radioisotope in the UI PET;
- ✓ To compare the costs of radioisotope production with the costs of purchasing a readymade product;
- ✓ To calculate the cost of in-house production of ^{89}Zr-trastuzumab radiopharmaceutical (three cases: production for 4, 7 and 10 patients).

Pharmacoeconomic analysis

Cost-benefit analysis

Objective:

- ✓ To assess the cost-benefit ratio of either testing patients with ^{89}Zr-trastuzumab PET/CT or biopsy as the comparison alternatives (breast cancer testing).

ECONOMIC ANALYSIS

Financial analysis

Pharmacoeconomic analysis

Cost analysis

Cost-benefit analysis

The production process was simulated based on literature data.

Unit costs sources: intentional marketing analysis, institute data review and analysis of the National Health Insurance Fund tariff costs.

Subject of the pharmacoeconomic analysis – **^{89}Zr-trastuzumab** (selection on the basis of the results of ***the preliminary analysis***)

ECONOMIC ANALYSIS

Cost analysis

Radioisotope (^{89}Zr-oxalate) cost (MKD)		
Purchased	>	Prepared in-house

The in-house production of zirconium-89 radioisotope is more profitable than its purchase.

Radiopharmaceutical (^{89}Zr-trastuzumab)	Case 1 (4 patients)	Case 2 (7 patients)	Case 3 (10 patients)
Cost per patient (EUR)	1 382	871	667

ECONOMIC ANALYSIS

Cost-benefit analysis

Case 1

Alternative	Cost per patient (EUR)	Net benefit	Cost/benefit
^{89}Zr-trastuzumab	1 382		
Biopsy	362	1 020	3.8

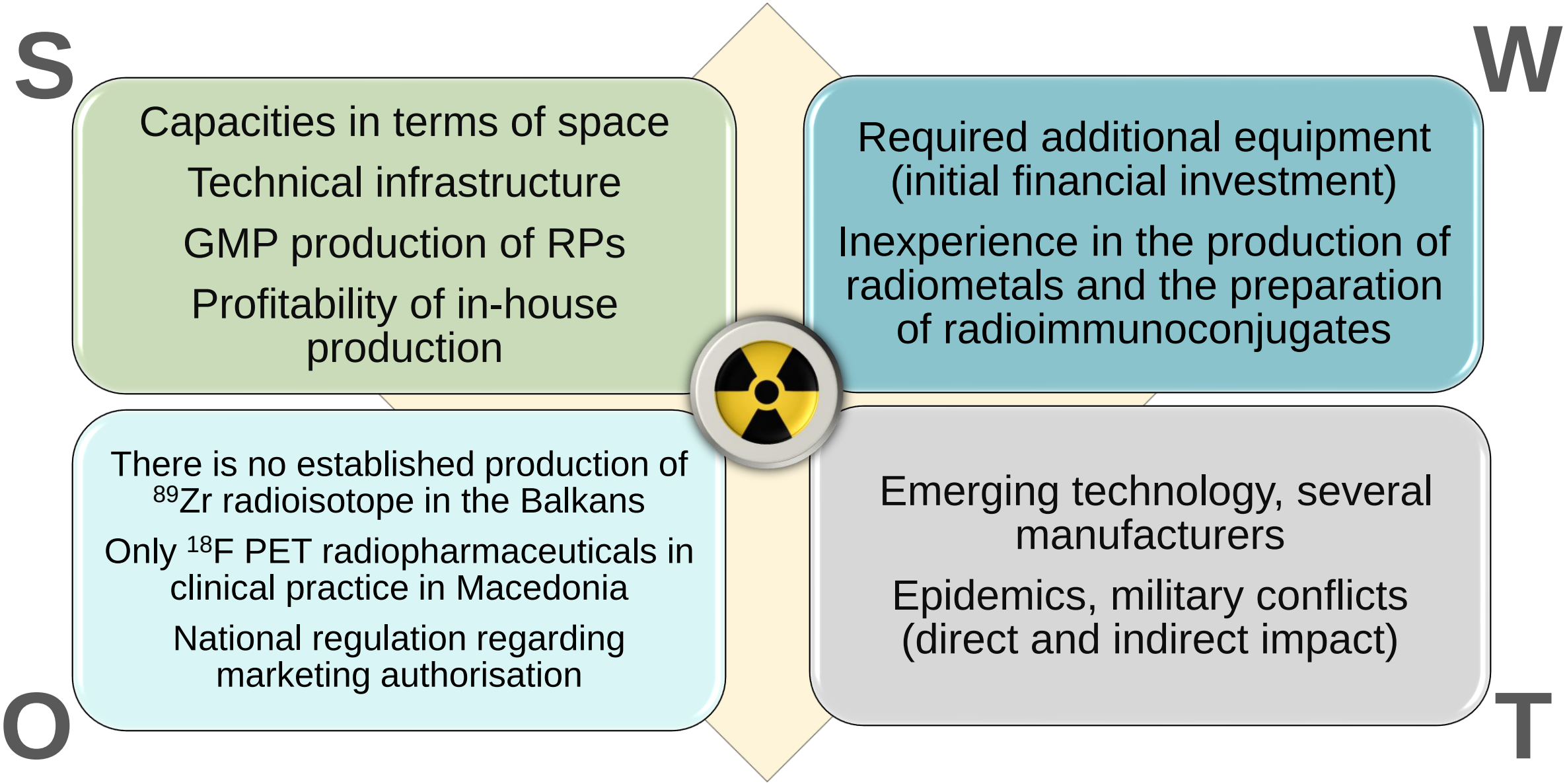
Case 2

Alternative	Cost per patient (EUR)	Net benefit	Cost/benefit
^{89}Zr-trastuzumab	871		
Biopsy	362	509	2.4

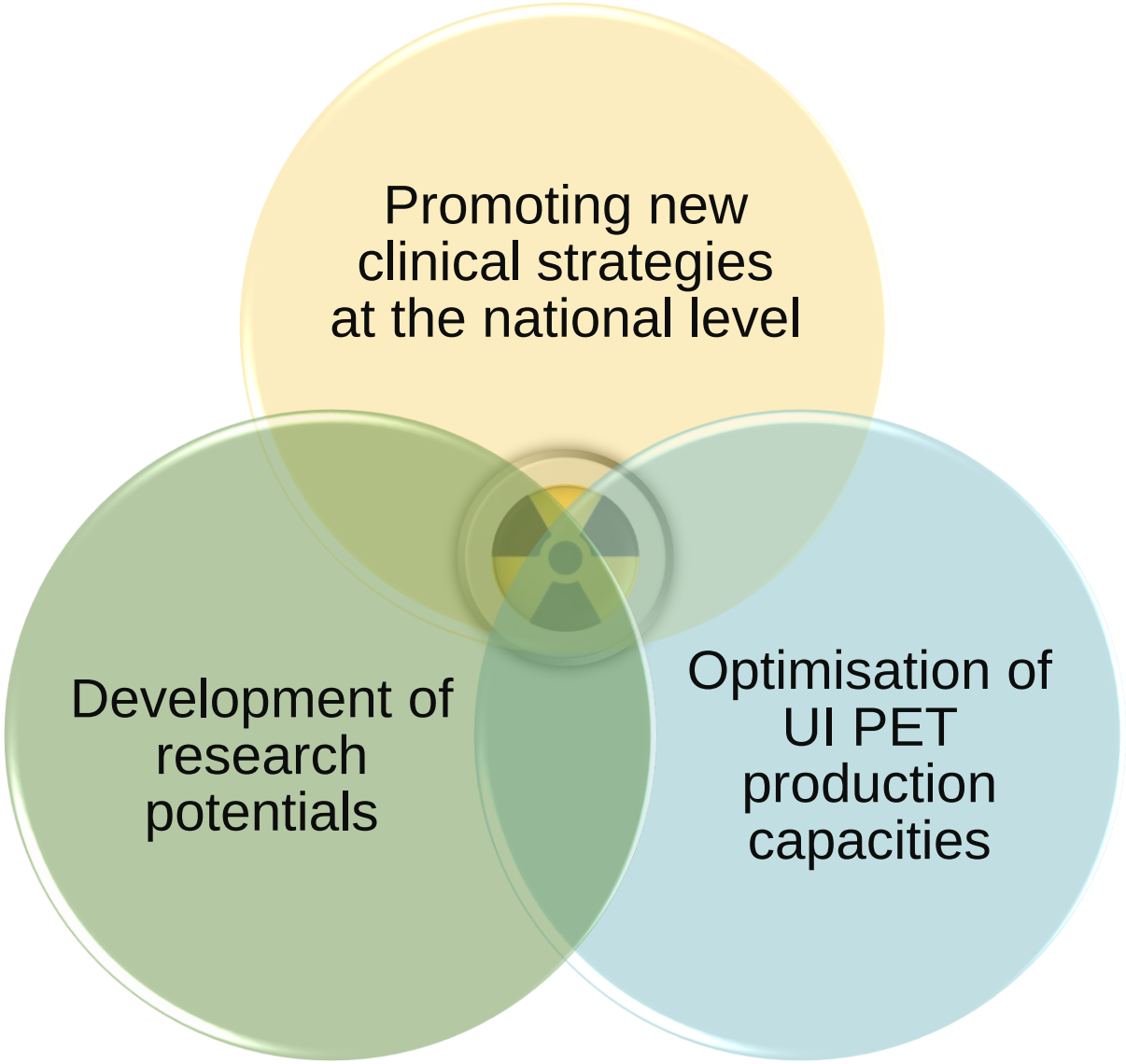
Case 3

Alternative	Cost per patient (EUR)	Net benefit	Cost/benefit
^{89}Zr-trastuzumab	667		
Biopsy	362	305	1.84

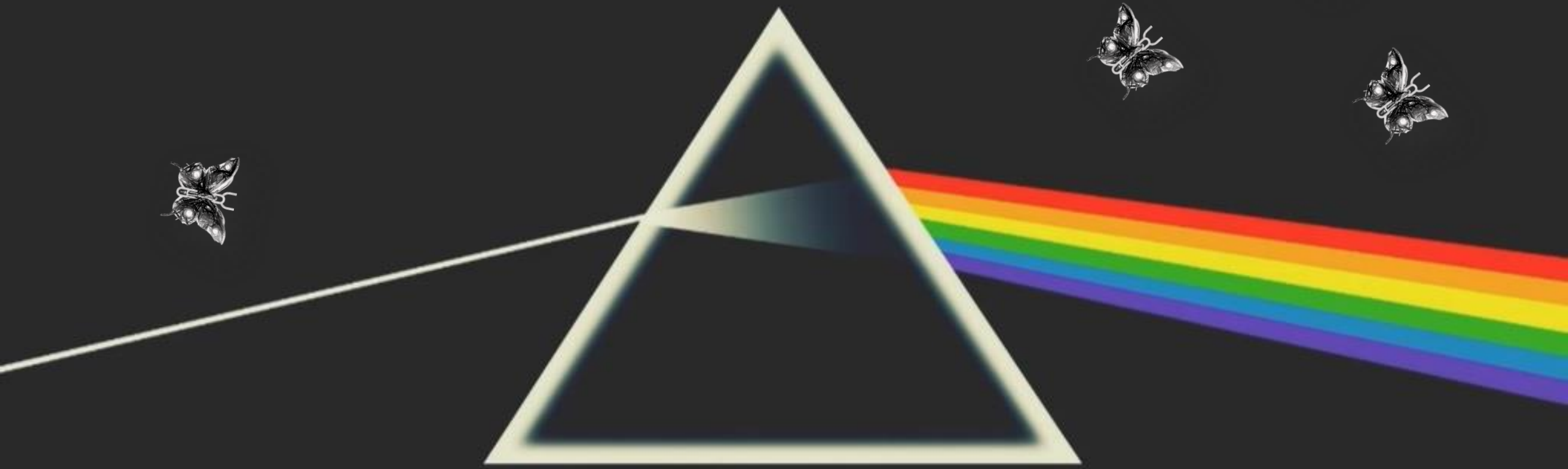
REVIEW AND ANALYSIS OF ALL DATA



FEASIBILITY CONCLUSION



Feasibility study...



... an opportunity to look at the other side