

HTx – 3rd Consortium Meeting

24-25 March 2021

Case Study 3

A two stage model for individualized predictions
under several treatment options for RRMS

Konstantina Chalkou, University of Bern



Relapsing-remitting Multiple Sclerosis RRMS



Multiple sclerosis (MS) - an immune-mediated disease of the central nervous system

Relapsing-remitting multiple sclerosis (RRMS): The most common subtype

Which treatment is the best for a specific patient?



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Relapsing-remitting Multiple Sclerosis (RRMS)

One size does not fit all

Treatment choice is (or should be) personalised

Not all patients have the same response to the same treatment

Heterogeneous Treatment Effects

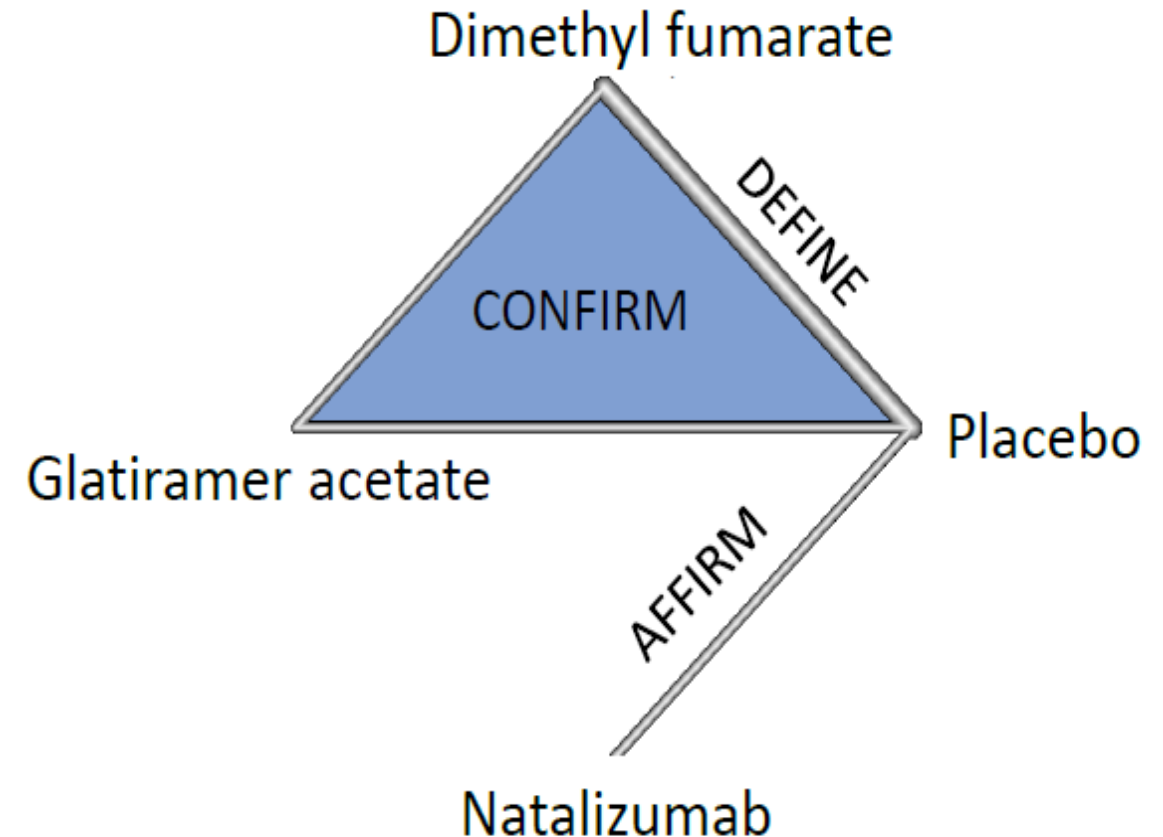
So, the optimal treatment depends on patients characteristics



**Risk
Modelling
approach**

Data RCTs

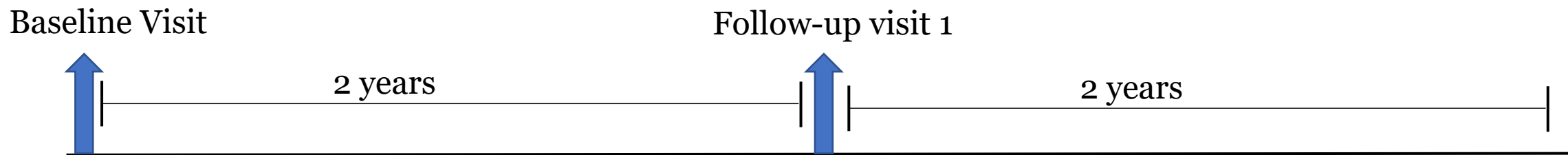
- 3 randomized clinical trials (phase III), 2990 observations in total
- **Disease:** Relapsing-remitting Multiple Sclerosis (MS)
- **Outcome:** Relapse within 2 years



Data

Observational study – Swiss MS Cohort study (SMSC)

- **Inclusion criteria:** Patients with confirmed RRMS and at least two-year follow-up period from the baseline visit date
- **Patients:** 935 patients, each one with 1, 2, or 3 treatment cycles (i.e. repeated measures)



- **Observations:** 1752 follow-up cycles

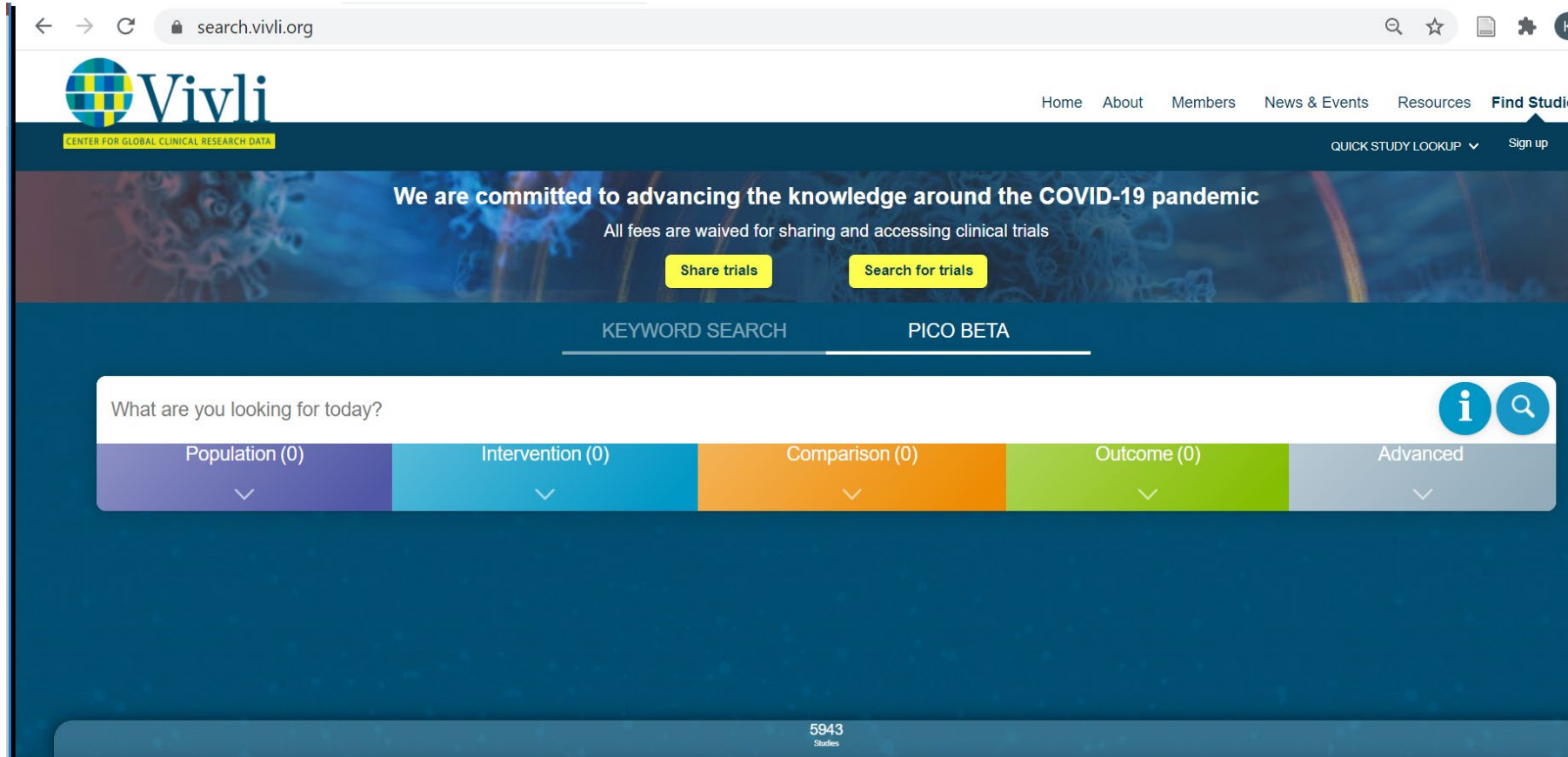


Data

New Dataset Obtained!



3 new RCTs with
IPD data via Vivli.org



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Treatments

Dimethyl
Fumarate

Glatiramer
acetate

Natalizumab

Placebo

Predicted
Outcome
A

Predicted
Outcome
B

Predicted
Outcome
C

Predicted
Outcome
D

Relative treatment
effects

Patient
characteristics

IPD from the
same RCTs

Network meta-
regression
methods

Prognostic
modelling
methods

Risk score
the probability
of the outcome
at baseline

IPD from RCTs

Internal Model

**Re-submitted in Statistics in
Medicine**

R-shiny app

Prevention of relapses in patients with Relapsing-Remitting Multiple Sclerosis

Age (years)
18 60
18 23 28 33 38 43 48 53 58 60

☐ Male
☐ White
☐ Prior treatment

Baseline EDSS
0 6
0 1 2 3 4 5 6

Years since onset of symptoms
0 45
0 5 10 15 20 25 30 35 40 45

Number of relapses the last 1 year
0 20
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

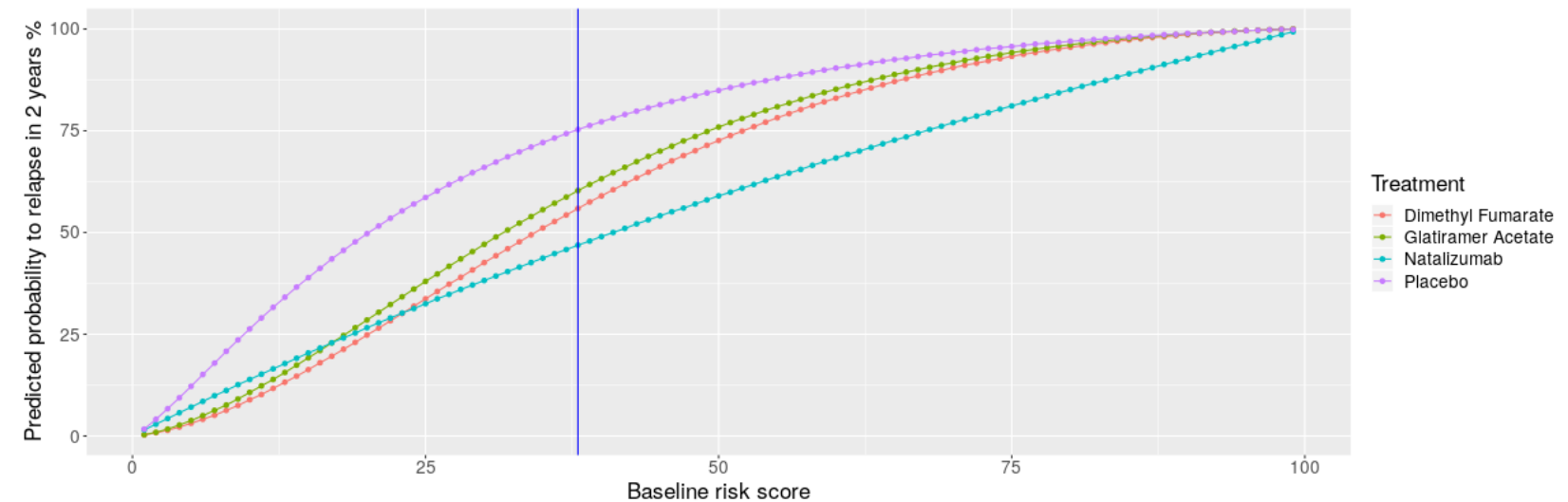
Months since last relapse
1

Baseline Timed 25-Foot Walk
1

Baseline PASAT 3
0 80
0 8 16 24 32 40 48 56 64 72 80

Your baseline risk score is 38

Plot of predicted probabilities to relapse in two years



Predicted probabilities to relapse in two years

Dimethyl Fumarate - 56 % / Glatiramer Acetate - 60 % / Natalizumab - 47 % / Placebo - 75 %

Ranking of predicted probabilities to relapse in two years

1. The lowest probability to relapse is under treatment:
Natalizumab with 46.9 % probability to relapse.
2. Second best choice based on the probability to relapse:
Dimethyl Fumarate with 55.9 % probability to relapse.
3. The treatment that follows is:
Glatiramer Acetate with 60.3 % probability to relapse.
4. The treatment with the highest probability to relapse is:
Placebo with 75.3 % probability to relapse

Github repository



← → ↺ github.com/htx-r/Reproduce-results-from-papers



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Chalkou Prognostic model Paper upload

7a0c362 on Sep 25, 2020 ⌚ 8 commits



ATwoStagePredictionModelMultiple... Prognostic model Paper upload

5 months ago



PrognosticModelIRRMS Prognostic model Paper upload

5 months ago

About

No description, website, or topics provided.

Releases

No releases published

Packages

No packages published

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the probability
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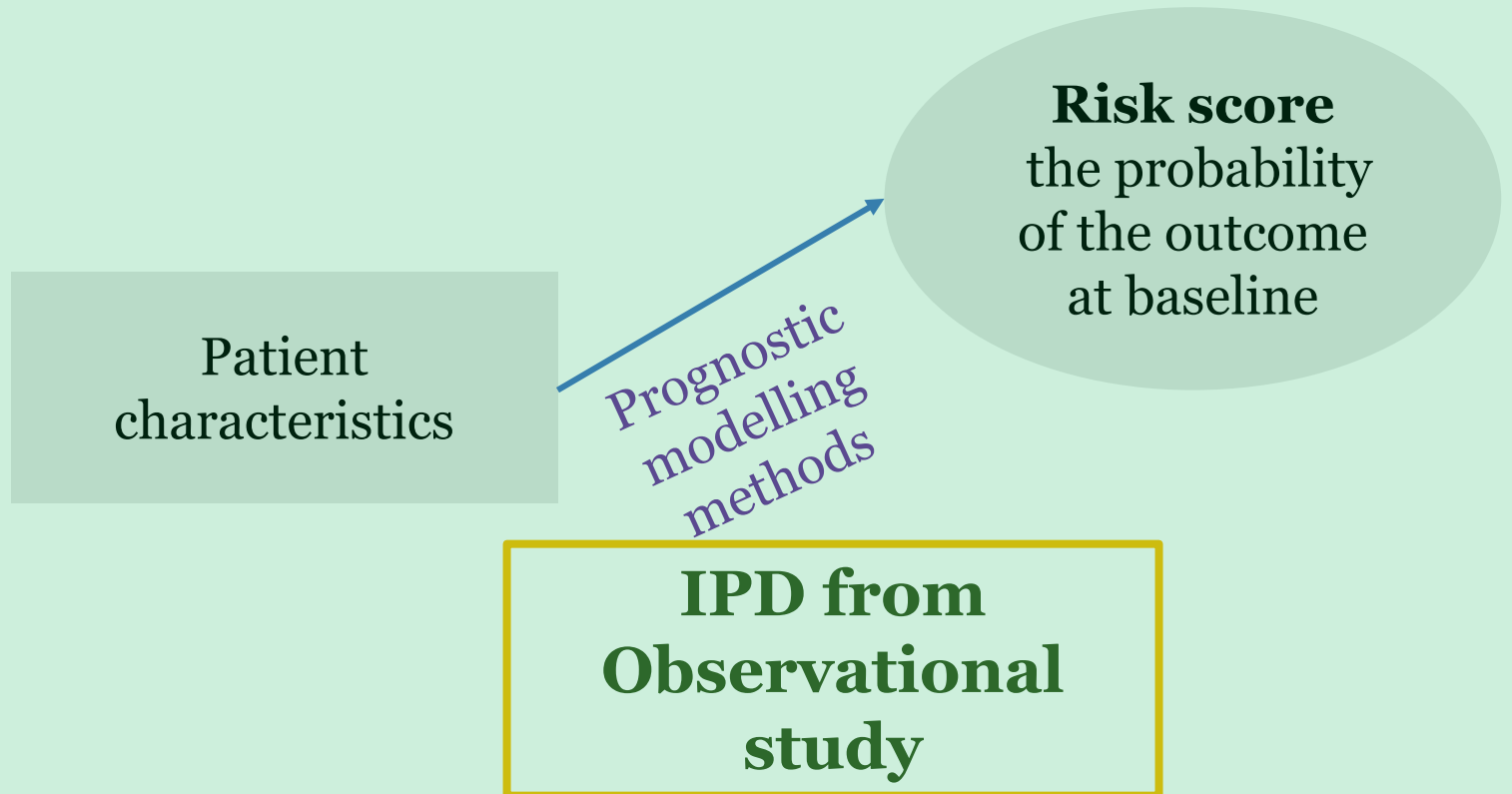
External Model

Ready

**IPD from
Observational
study**

Prognostic model

Ready for submission in BMC diagnostic and prognostic research



R-shiny app

Prevention of relapses in patients with Relapsing-Remitting Multiple Sclerosis

Age (years)
17 38 80
17 24 31 38 45 52 59 66 73 80

Disease Duration (years)
2.4

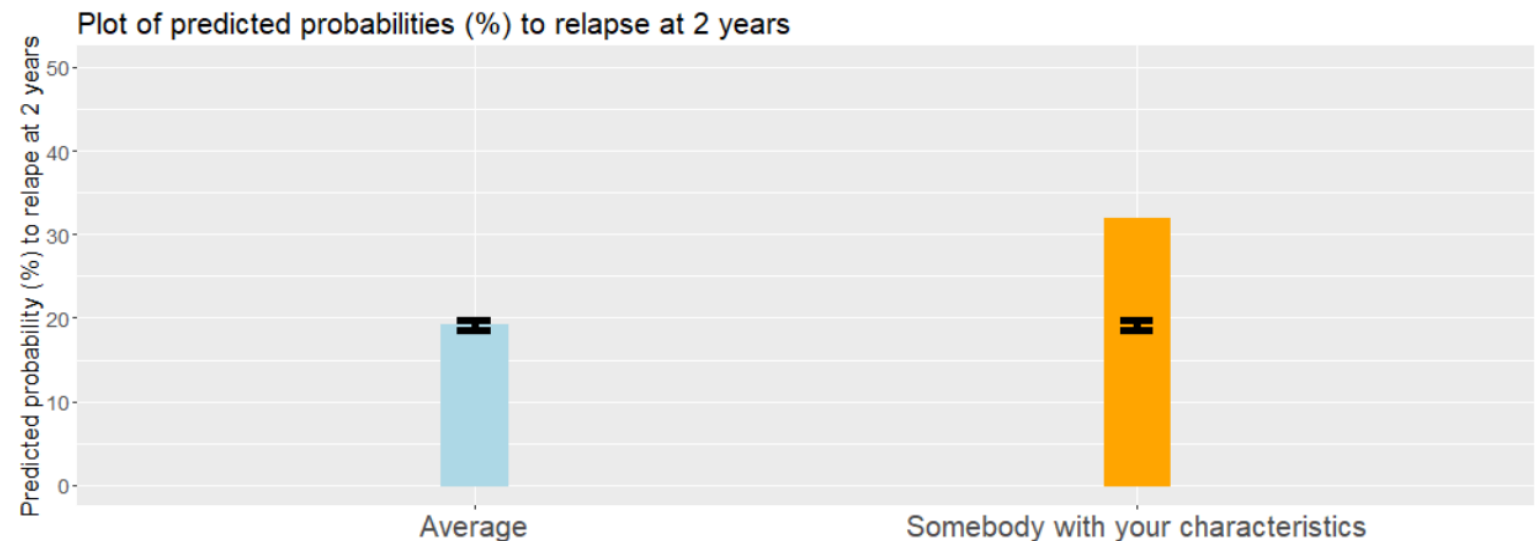
EDSS
0 1 7
0 1 2 3 4 5 6 7

☒ Number of Gadolinium enhanced lesions > 0
☐ 1 prior relapse
☒ 2 or more prior relapses

Months since last relapse
4.2

☐ Treatment Naive
☒ Female

Your risk to relapse at 2 years is 32 %



Numerical Results:

The average predicted probability (%) to relapse at 2 years is 19.2 with 95% C.I. (18.6, 19.7)

Somebody with your characteristics has 32 % predicted probability (%) to relapse at 2 years

Your predicted probability (%) to relapse at 2 years is 12.8 % higher than the average



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IPD from RCTs



AD from RCTs

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External Model

Ongoing work

IPD from
Observational
study

IPD and AD from RCTs and real-world data

Presentations during the last year



1. ISCB conference, 2020
2. Swiss Public Health Conference in Lucerne, 2020
3. Webinar CS 3 HTx, 2020
4. Virtual ISPOR Europe 2020 Conference, 2020



Next Steps

Development of **evaluation methods** for heterogeneous treatment effects prediction models using **decision curve analysis**

Cost-effectiveness analysis, in collaboration with
UoY – Andrea Manca

