Trials and tribulations – economic evaluation, study design and statistics

Prepared for Global Statistics Team

Contained in this presentation

- What is a health economist and who are our target audience
- What to collect from trials, utilities, costs, cross-overs, duration
- Level of complexity- getting it right
- Staying ahead of the game

What is a Health Economist?

- Like Frankenstein's monster, only nicer
- Parts of everything
  - Economics
  - Clinical study design
  - Medical sciences
  - Biostatistics
  - Psychology
  - Business analyst

Who are our target Audience?

- National reimbursement Committees
  - Clinical dominates
  - Health economics needs to be correct but understandable
- Pharmacy budget holders
- Insurers
- Clinicians
- Internal customers i.e. brand managers

Who are our target Audience – international?

- Each country has a subtly different approach
  - Sophisticated HTA environment
    - Differences within these i.e. Individual Patient Data vs Individual Patient Data
    - Trialists versus modellers
      - Trialists believe the RCT is gold standard and mistrust or suspicious of models
      - Modellers focus on models and their ability to capture relevant data and uncertainty. RCT less important
  - Developing HTA environments
    - Asia want “local data”
    - May not have evaluation capacity
- One size doesn’t necessary fit all. Do we ever need two models?

Designing a clinical study with cost effectiveness in mind – registration versus reimbursement

Issue	Answer	i.e.
Comparator/s	multiple for reimbursement; fewer registration and even placebo	Alimta NSCLC
Primary endpoints	Ask the FDA, EMEA	Peak VO_2 versus NYHA classification in CHF
Statistical power and multiple comparisons	to show a difference in the registration endpoint – not economic endpoints	Hospital admissions
Countries in the study	need for trial participants vs where can we get important economic data	Scandinavia; UK; Australia; Mexico; Korea

Designing a clinical study with cost effectiveness in mind – Deciding what to collect - Utilities

- Utilities? i.e. EQ-5D, AQoL, HUI, SF-36
  - Payers want these from within studies
    - What if trial isn't powered to show a difference?
    - What if the condition isn't sensitive to instruments?
    - How do you interpret these results?
  - Some countries want localised utilities
    - Can apply local country scoring algorithm to the study results
    - Can use the countries own results although as this is a retrospective sub-group analysis may not be valid

EQ-5D L3

EQ-5D l3

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care
I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

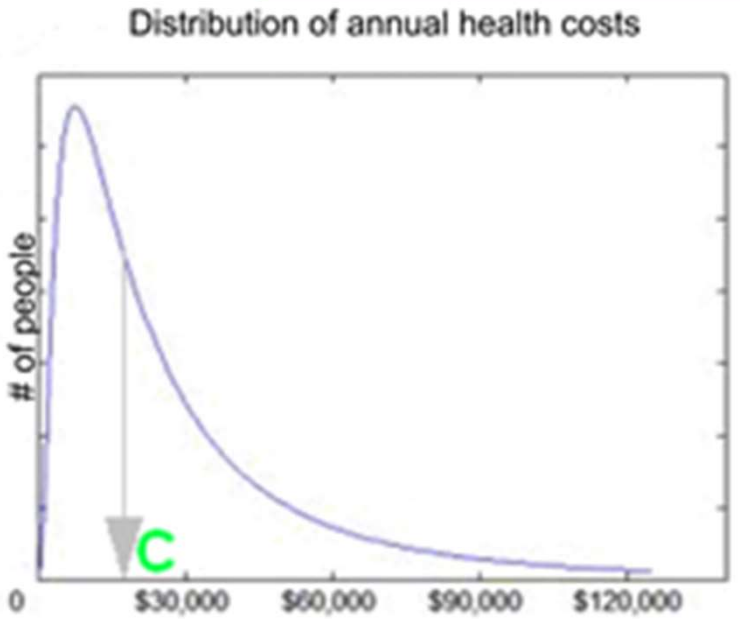
Usual Activities (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort
I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression
I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

Designing a clinical study with cost effectiveness in mind – Deciding what to collect - Cost

- Cost data - effect of cost outliers
  - High cost outliers can randomly occur on one arm of the study
  - Need to decide a priori how to deal with this



Example: HIV study

- Control arm cost range $1,000 to $10,000 per patient
- Intervention arm cost range $1,000 to $10,000 per patient
  However one patient $200,000
- Makes costs higher on the Intervention arm

Designing a clinical study with cost effectiveness in mind – - cross over and treatment

Cross overs and their clinical treatment

Example: Oncology

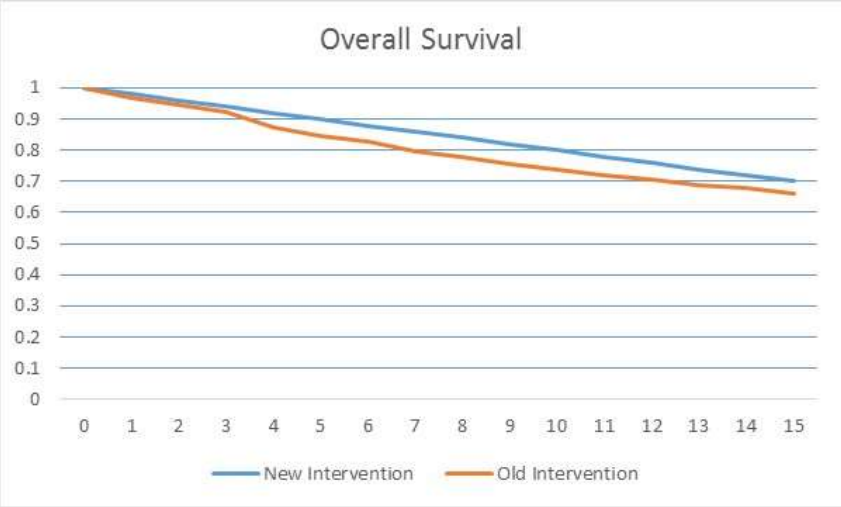
- If collect survival and progression free survival to end of follow up also collect all relevant costs
- In example collecting cross overs reducing additional incremental costs from $17,000 to $13,500 per patient
- Appropriate statistical treatment of cross-overs is also important

Impact of cross over treatment

	New therapy	Old therapy	Incremental cost
Cost of chemotherapy	$20,000	$3,000	$17,000
Percent cross over at failure	20%	20%	$0
Cost per patient without cross over	$20,000	$3,000	$17,000
Cost per patient with cross over	$20,600	$7,000	$13,600

Designing a clinical study with cost effectiveness in mind – Deciding what to collect - Duration

- Long enough to capture important outcomes



What will be the difference in survival after the trial? convergence, extrapolation, speculation

International differences

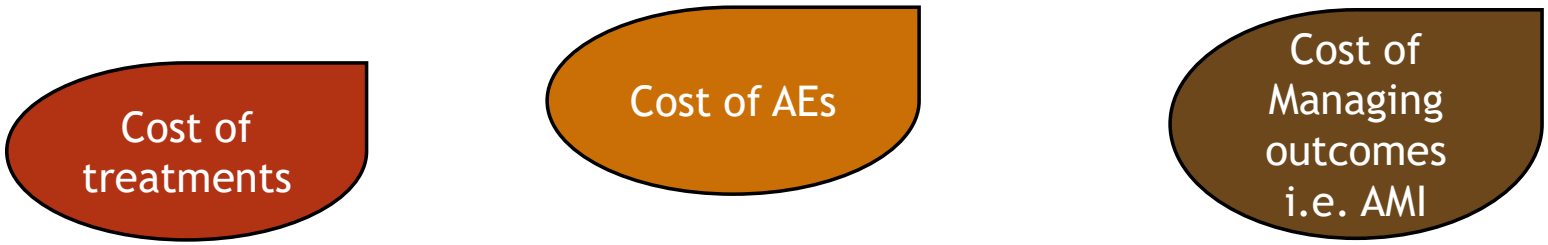
- Separate for each country
- Useful for localising global models

Variable	Approach
Utilities	Local from trial or separate study - preference weights
Body weight	Local – weight
AEs and their pattern of treatment	Local - and can vary from country to country
Other health care resources	Local - From within trial

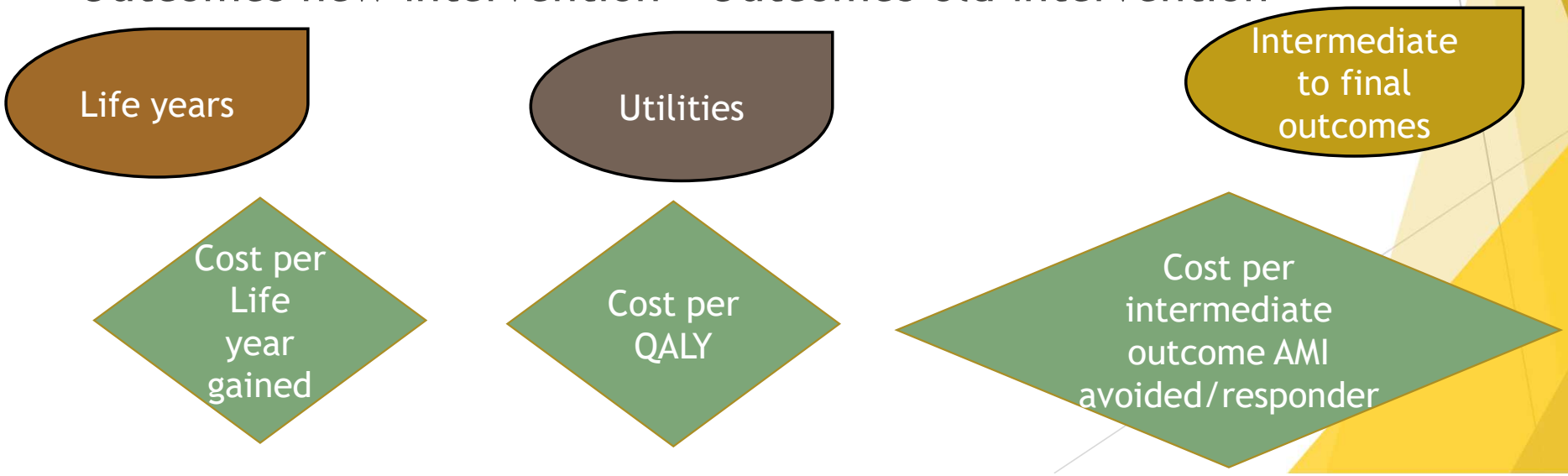
Trial outputs ➡ model inputs

- Exact dosing per patient to cost out doses
- Adverse effects to cost out adverse effects
- Cross overs and the treatment they received
- Utilities
- Survival if its an issue
- Sub-groups – dosing Tulicity Korea going with 0.75mg does only and ignoring 1.5mg
- Meta-analysis
- Indirect analysis
  - Bucher vs network analysis
  - To match other study populations or outcomes i.e. PANNS responders vs mean change

Cost effectiveness ratio



$$\frac{\text{Costs New intervention} - \text{Costs old intervention}}{\text{Outcomes new intervention} - \text{Outcomes old intervention}}$$

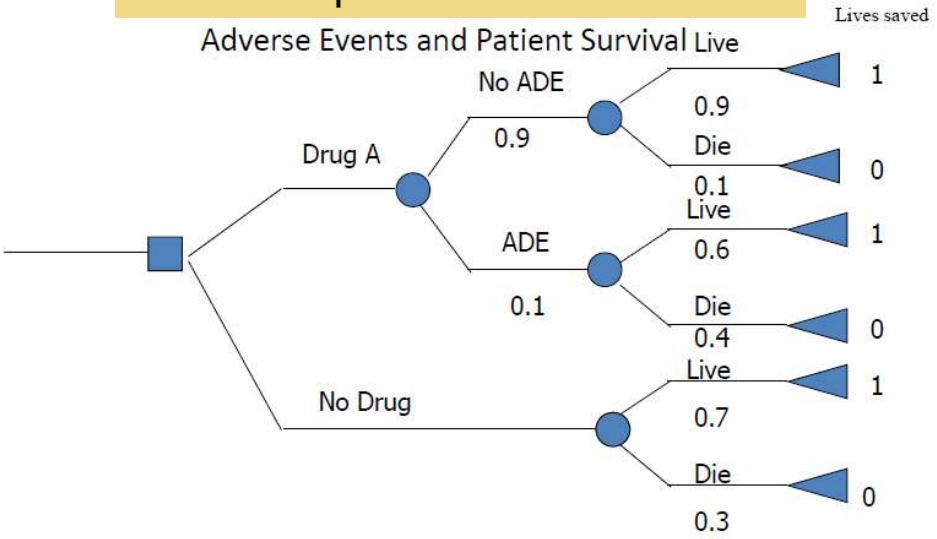


Different types of economic evaluation

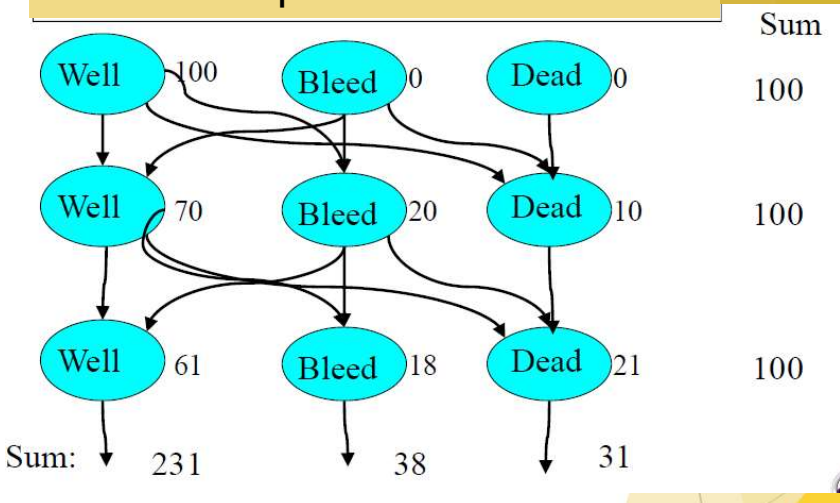
	Costs	Outcomes	Expressed as example
Cost analysis	$ Health care	None	New treatment cost saving
Cost minimisation analysis	$ Health care	Natural units and equal	New treatment cost equal or saving and outcomes equal
Cost effectiveness analysis	$ Health care	Natural units and superior	Cost per life year saved Cost per additional Objective Response
Cost utility analysis	$ Health care	Utilities/QALYs	Cost per QALY
Cost benefit analysis	$ Health care plus indirect at times	$ Costs	Benefits exceed cost by X

Different types of models

Simple Decision Tree



Markov process - warfarin



Economic sub-studies/phase IV studies when data are not collected in the RCT

- Can collect utility values and costs
  - Health states and costs outside of the trial outcomes – i.e. longer term outcomes
  - Low incident health outcomes and costs – i.e. adverse events
  - In countries which require local utility values and are not covered by the registration studies i.e. Korea
- Evidence on prevalence of the condition
- Natural progression of the disease/condition

What are the limits of understanding of non statisticians primarily payers and company staff/consultants

Some economists don't understand

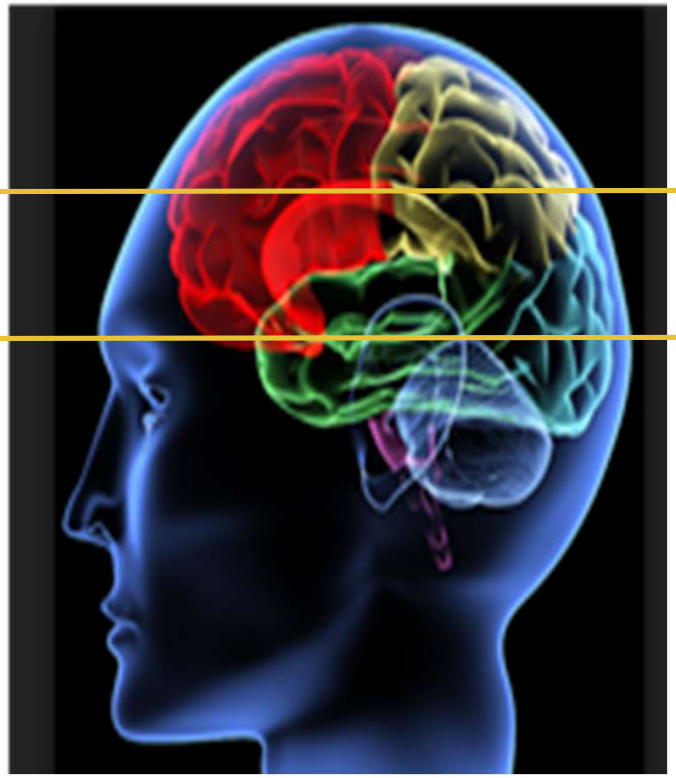
Extremely complex modelling and complex programming – cutting edge methods, flexibility constrained

Clinicians don't understand

Very complex modelling – includes more than the key variables

Everyone understands

Simple to intermediate complexity models – includes key variables; flexible



Programming complexity

Complex approach example

- Vial dosage (how much they are administered)
  - =IF(C11="","",IF(OFFSET($U$9,0,MATCH(C11,$X$7:$AP$7,0)+2)=1,ROUNDUP(K11/I11,0)*I11,IF(OFFSET($U$9,0,MATCH(C11,$X$7:$AP$7,0)+2)>2,N11*I11,IF(AND(C10=C11,(OFFSET($U$9,0,MATCH(C11,$X$7:$AP$7,0)+2)=2)),IF(L10>K10,0,ROUNDUP((K11-L10)/I11,0)*I11),IF(ROUNDUP(K11/I11,0)*H11<(ROUNDDOWN(K11/I11,0)*H11)+ROUNDUP((ROUNDUP(K11-(ROUNDDOWN(K11/I11,0)*I11),0)/I12),0)*H12,ROUNDUP(K11/I11,0)*I11,ROUNDDOWN(K11/I11,0)*I11)))))
- Body weight
  - =IF(C11="","",(OFFSET(Resource!$J$17,MATCH('Drug wastage'!C11,Resource!$M$19:$M$37,0)+1,0)))
- Total mgs
  - =IF(F11="","",F11*G11)
- Price
  - =IF(ISBLANK(DrugCosts!H13),"",DrugCosts!H13)

Simple approach example

- Vial dosage (how much they are administered)
- Body weight
- Total mgs

Simulation of trial outcomes versus directly using trial outcomes

- Multiple comparisons in one analysis
  - Network analysis
  - Simulate clinical outcomes

  Pros
  - Transitive
  - Same outcomes and costs for the primary intervention

  Cons
  - Model is different from trial

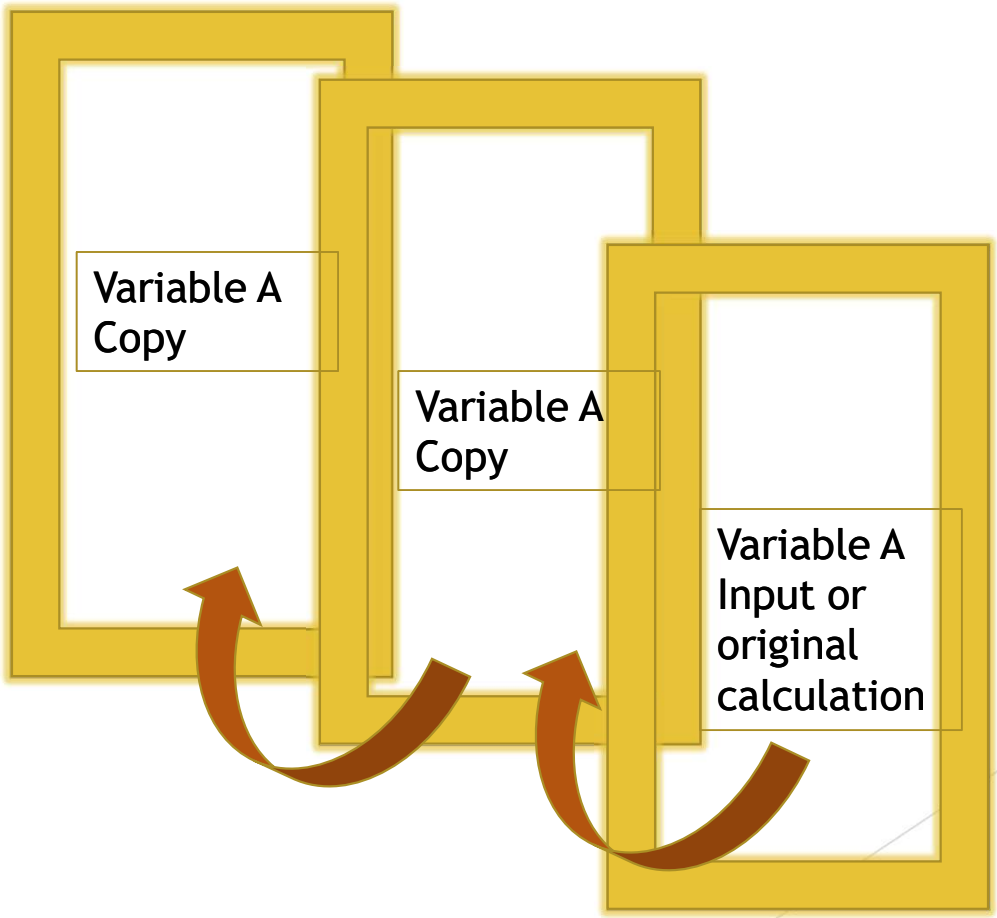
- Multiple comparisons in a series of bilateral comparisons
  - Indirect analysis via common reference arm
  - Trial based analysis

  Pros
  - Model outcomes are the same as the trials

  Cons
  - Not transitive

Repeat variables multiple times

"Shadow variables adds unnecessarily Complexity"



Complex versus simple models

Highly complex pros

- Can include more detail regarding CE of therapy ✓
- Can contain built in variable choices ✓
- No criticism that it is too simplistic ✓
- Justify consulting fee get moneys worth ✓
- Show skill and commitment ✓

Highly complex cons

- Many of payers don't understand what they are seeing ×
- May be rejected as "black box" i.e. Core model in Australia ×
- Confusion in internal company communication ×
- Errors don't get picked up. ×
- Evaluation process difficult ×

10 Rules for modelling

"A model is a simplification of reality – we need to see the wood for the trees"

1. Once - Inputs variables only once
2. Learn - Continuous learning
3. Simple – KISS (Keep it Simple Stupid)
4. Reference – Reference all sources
5. Manual - Provide a technical manual
6. Valid - Model should be validated by the trial outcomes
7. Flexibility - Flexibility for the user, not constrained flexibility
8. Time - Running time should not be excessive
9. Size- Over 50mb becomes a problem
10. Cost effective – results should be cost effective.

Getting ahead of the game

Issue	Solution	i.e.
Established intermediate outcome	Which outcome, power this, maybe secondary outcome	NYHA responders
Duration	As long as possible	Survival
Utilities	Are they sensitive – go to sub-study	EQ-5D
Collect all relevant health care resources	Split by country	Hospital admission; cross over to chemotherapy
Comparators	As many as practical then plan indirect analysis	
What data are required and what are the gaps	Early model to determine data requirements and gaps	Current vaccine modelling

Thank you

Questions