Content

Part IV

On the need of aggregating evidence across multiple clinical studies

Part V
Aggregating evidence using argumentation

(Based on the work *"Aggregating evidence about the positive and negative effects of treatments"* by Hunter and Williams (2012))

Hunter, A. and Williams, M., 2012. Aggregating evidence about the positive and negative effects of treatments. Artificial intelligence in medicine, 56(3), pp.173-190.

Aggregation technologies

Aggregation technologies are needed for:

- Making evidence-based recommendations based on large repositories of complex, rapidly expanding, incomplete and inconsistent evidence.
- Overcoming limitations such as:
  - out-dated guidelines/systematic reviews
  - dealing with huge amounts of existing and new evidence
  - conflicting guidelines
- Considering particular cases: guideline recommendations often interprets general populations, but not cases with specific features (e.g. patients from a particular ethnic group, age, precondition, etc.).
- Offering tools to support evidence-based decisions, to draft systematic reviews and guidelines, and to help resolving conflicts in the available evidence.

Aggregation of CT evidence

- When evidence is aggregated in guideline/systematic reviews development, the aim is to determine whether one treatment is better than another.
- There are two main dimensions to be considered:
  - *Outcomes*:
    - e.g. is one treatment more efficacious than another, does one treatment have more side-effects than the other?
  - *Quality of the evidence*:
    - e.g. is the evidence supporting the superiority of a treatment over another, based on non-statistically significant studies?

Evidence Table

Where:

NT: no treatment

BB: beta-blocker

PG: prostaglandin analogue

SY: sympathomimetic

CA: carbonic anhydrase inhibitor

	Left	Right	Outcome indicator	Value	Net	Sig	Type
e_{01}	BB	NT	visual field prog	0.77	>	no	MA
e_{02}	BB	NT	change in IOP	-2.88	>	yes	MA
e_{03}	BB	NT	respiratory prob	3.06	<	no	MA
e_{04}	BB	NT	cardio prob	9.17	<	no	MA
e_{05}	PG	BB	change in IOP	-1.32	>	yes	MA
e_{06}	PG	BB	acceptable IOP	1.54	>	yes	MA
e_{07}	PG	BB	respiratory prob	0.59	>	yes	MA
e_{08}	PG	BB	cardio prob	0.87	>	no	MA
e_{09}	PG	BB	allergy prob	1.25	<	no	MA
e_{10}	PG	BB	hyperaemia	3.59	<	yes	MA
e_{11}	PG	SY	change in IOP	-2.21	>	yes	MA
e_{12}	PG	SY	allergic prob	0.03	>	yes	MA
e_{13}	PG	SY	hyperaemia	1.01	<	no	MA
e_{14}	CA	NT	convert to COAG	0.77	>	no	MA
e_{15}	CA	NT	visual field prog	0.69	>	no	MA
e_{16}	CA	NT	IOP > 35mmHg	0.08	>	yes	MA
e_{17}	CA	BB	hyperaemia	6.42	<	no	MA
e_{18}	SY	BB	visual field prog	0.92	>	no	MA
e_{19}	SY	BB	change in IOP	-0.25	>	no	MA
e_{20}	SY	BB	allergic prob	41.00	<	yes	MA
e_{21}	SY	BB	drowsiness	1.21	<	no	MA

Each row is a meta-analysis from the NICE glaucoma GL for patients with raised IOP (i.e. at risk of glaucoma and thus, irreversible damage to the optic nerve and retina).

Outcome indicators interpretations

- The outcome indicator is what is being measured, and the value is the value of that measure determined by:
  - *Relative Risk*: proportion of patients who presented an outcome indicator (i.e. “mortality”, “stroke”) in the left arm divided by the proportion of patients presenting it in the right arm.
- Other value Interpretations (e.g. for the glaucoma case):
  - Change in IOP: if value < 0, the left arm is superior, otherwise it is inferior.
  - Acceptable IOP: is a desirable outcome. If value > 1, then the left arm is superior, otherwise it is inferior.
  - Other outcome indicators (i.e. for respiratory problems, cardiovascular problems, etc.), which are undesirable. If value < 1, then the left arm is superior, otherwise it is inferior.

Inductive arguments

- Set of evidence EVIDENCE = {e_1 , .., e_n} concerning a pair of treatments {τ_1, τ_2}
- Interpretations:
  - $\tau_1 > \tau_2$: the evidence supports the claim that treatment τ_1 is *superior* to τ_2
  - $\tau_1 \sim \tau_2$: the evidence supports the claim that treatment τ_1 is *equivalent* to τ_2
  - $\tau_1 < \tau_2$: the evidence supports the claim that treatment τ_1 is *inferior* to τ_2

Definitions

Inference rules, where $X \subseteq$ evidence and $X \neq \emptyset$:

- If $X \subseteq$ SUPERIOR, then $\tau_1 > \tau_2$
- If $X \subseteq$ EQUITABLE, then $\tau_1 \sim \tau_2$
- If $X \subseteq$ INFERIOR, then $\tau_1 < \tau_2$

Inductive argument is a tuple $<X, \epsilon>$, such that ϵ follows from using one of the inference rules. X is called the support and ϵ the claim of the argument.

Arg(Evidence)

Given a set *Evidence*, *Arg(Evidence)* is the set of inductive arguments that can be generated from the evidence according to the previous definition.

Example of inductive arguments

	Left	Right	Outcome indicator	Value	Net	Sig	Type
e_1	ACE	CCB	mortality	1.04	$<$	no	MA
e_2	ACE	CCB	stroke	1.15	$<$	yes	MA
e_3	ACE	CCB	heart failure	0.84	$>$	yes	MA
e_4	ACE	CCB	diabetes	0.85	$>$	yes	MA

$$\langle\{e_3\}, \text{ACE} > \text{CCB}\rangle \qquad \langle\{e_1\}, \text{ACE} < \text{CCB}\rangle$$
$$\langle\{e_4\}, \text{ACE} > \text{CCB}\rangle \qquad \langle\{e_2\}, \text{ACE} < \text{CCB}\rangle$$
$$\langle\{e_3, e_4\}, \text{ACE} > \text{CCB}\rangle \qquad \langle\{e_1, e_2\}, \text{ACE} < \text{CCB}\rangle$$

Results from the NICE Hypertension Guideline concerning angiotensin-converting inhibitors (ACE) and calcium channel blockers (CCB).

Results

- For an item of evidence e, the result of the evidence is the pair: (*OutcomeIndicator, Value*)

	Left	Right	Outcome indicator	Value	Net	Sig	Type
e_{81}	CP	NC	breast cancer	1.04	<	yes	RCT
e_{82}	CP	NC	ovarian cancer	0.99	>	yes	MA
e_{83}	CP	NC	pregnancy	0.05	>	yes	RCT
e_{84}	CP	NC	thrombosis	1.02	<	yes	MA

Results	ARG(EVIDENCE)	Result(A_i)
e_{81} has result (breast cancer, 1.04) e_{82} has result (ovarian cancer, 0.99) e_{83} has result (pregnancy, 0.05) e_{84} has result (thrombosis, 1.02)	$A_1 = \langle\{e82, e83\}, CP > NC\rangle$ $A_2 = \langle\{e82\}, CP > NC\rangle$ $A_3 = \langle\{e83\}, CP > NC\rangle$ $A_4 = \langle\{e81, e84\}, CP < NC\rangle$ $A_5 = \langle\{e81\}, CP < NC\rangle$ $A_6 = \langle\{e84\}, CP < NC\rangle$	Results(A_1) = {(ovarian cancer, 0.99), (pregnancy, 0.05)} Results(A_2) = {(ovarian cancer, 0.99)} Results(A_3) = {(pregnancy, 0.05)}) Results(A_4) = {(breast cancer, 1.04), (thrombosis, 1.02)} Results(A_5) = {(breast cancer, 1.04)} Results(A_6) = {(thrombosis, 1.02)}

Hunter and Williams (2012)

Benefits

Let A be an inductive argument where Claim(A) is $\tau_1 > \tau_2$, $\tau_1 \sim \tau_2$, or $\tau_1 < \tau_2$. The Benefits function is defined as:

$$\text{Benefits}(A) = \begin{cases} \text{Results}(A) \text{ when Claim}(A) \neq \tau_1 < \tau_2 \\ \text{Normalize}(A) \text{ when Claim}(A) = \tau_1 < \tau_2 \end{cases}$$

	Left	Right	Outcome indicator	Value	Net	Sig	Type
e_{81}	CP	NC	breast cancer	1.04	<	yes	RCT
e_{82}	CP	NC	ovarian cancer	0.99	>	yes	MA
e_{83}	CP	NC	pregnancy	0.05	>	yes	RCT
e_{84}	CP	NC	thrombosis	1.02	<	yes	MA

Result(Ai)	Benefit(Ai)
Results(A1) = {(ovarian cancer, 0.99), (pregnancy, 0.05)}	Benefits(A1) = {(ovarian cancer, 0.99), (pregnancy, 0.05)}
Results(A2) = {(ovarian cancer, 0.99)}	Benefits(A2) = {(ovarian cancer, 0.99)}
Results(A3) = {(pregnancy, 0.05)})	Benefits(A3) = {(pregnancy, 0.05)})
Results(A4) = {(breast cancer, 1.04), (thrombosis, 1.02)}	Benefits(A4) = {(breast cancer, 0.96), (thrombosis, 0.98)}
Results(A5) = {(breast cancer, 1.04)}	Benefits(A5) = {(breast cancer, 0.96)}
Results(A6) = {(thrombosis, 1.02)}	Benefits(A6) = {(thrombosis, 0.98)}

Benefits: interpretation

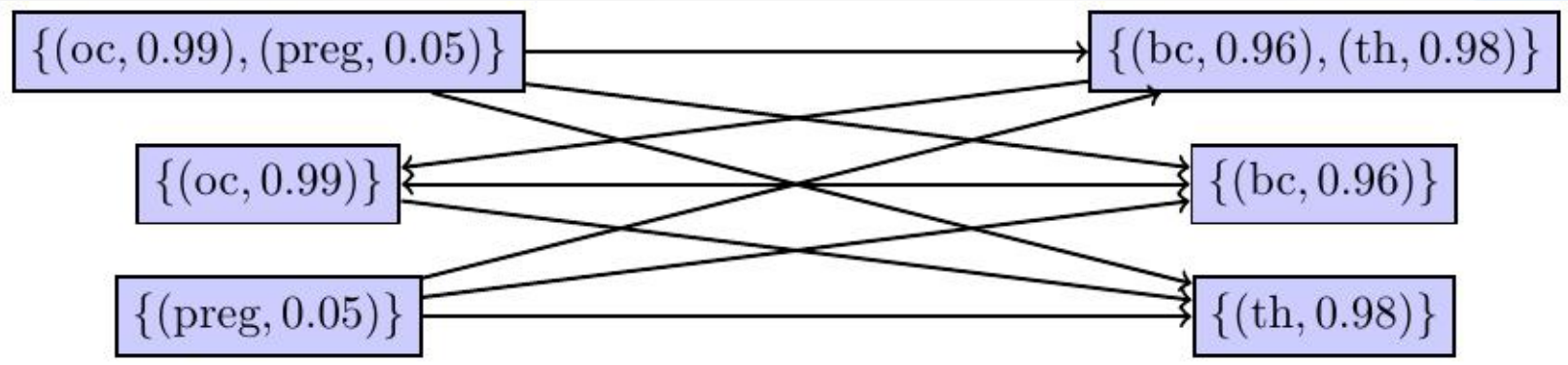
- A result (OutcomeIndicator, Value) is a benefit when:
  - The OutcomeIndicator is for something good (e.g. survival rate, etc.) and *Value* means that the left arm is better than the right arm:
    - e.g. for an outcome indicator measured in RR, value > 1), then (OutcomeIndicator, Value) is a benefit.
  - The OutcomeIndicator is for something bad (e.g. death rate, etc.) and *Value* means that the left arm is better than the right arm:
    - e.g. for an outcome indicator measured in RR, value < 1), then (OutcomeIndicator, Value) is a benefit.

Benefits preference relations

For arguments A_i, A_j:

- Benefits(A_i) $\succ$ Benefits(A_j) means that the results of A_i are preferred to the results of A_j
- The user would give the benefits preference relation
- Benefits graph:
  - Each node is the benefits for an argument
  - Each arc denotes that the benefits for the first node are preferred to the benefits of the second node

Benefits graph



$\text{Benefits}(A_1) \succ \text{Benefits}(A_4)$ $\text{Benefits}(A_4) \succ \text{Benefits}(A_2)$ $\text{Benefits}(A_3) \succ \text{Benefits}(A_4)$
$\text{Benefits}(A_1) \succ \text{Benefits}(A_5)$ $\text{Benefits}(A_2) \sim \text{Benefits}(A_5)$ $\text{Benefits}(A_3) \succ \text{Benefits}(A_5)$
$\text{Benefits}(A_1) \succ \text{Benefits}(A_6)$ $\text{Benefits}(A_2) \succ \text{Benefits}(A_6)$ $\text{Benefits}(A_3) \succ \text{Benefits}(A_6)$

Conflict and attacks

If the claim of argument A_i is ϵ_i and the claim of argument A_j is ϵj then A_i conflicts with A_j when:

- $\epsilon_i = \tau_1 > \tau_2$, and ($\epsilon j = \tau_1 \sim \tau_2$ or $\epsilon_j = \tau_1 < \tau_2$)
- $\epsilon_i = \tau_1 \sim \tau_2$, and ($\epsilon j = \tau_1 > \tau_2$ or $\epsilon_j = \tau_1 < \tau_2$)
- $\epsilon_i = \tau_1 < \tau_2$, and ($\epsilon j = \tau_1 > \tau_2$ or $\epsilon_j = \tau_1 \sim \tau_2$)

For any pair of arguments A_i and A_j, and a preference relation R, A_i attacks A_j with respect to R if A_i conflicts with A_j and A_j is not strictly preferred to A_i, according to R.

Inductive argument graph

Given a Topic = $\{\tau_1 , \tau_2\}$ and a set EVIDENCE, a inductive argument graph Arg(Evidence,Topic) in which:

- the set of nodes is the subset of Arg(Evidence) containing arguments with a claim in $\{\tau_1 > \tau_2, \tau_1 \sim \tau_2 , \tau_1 < \tau_2\}$
- the set of arcs is the attack relation given in the previous definition.

Example of an inductive argument graph

	Left	Right	Outcome indicator	Value	Net	Sig	Type
e_{81}	CP	NC	breast cancer	1.04	$<$	yes	RCT
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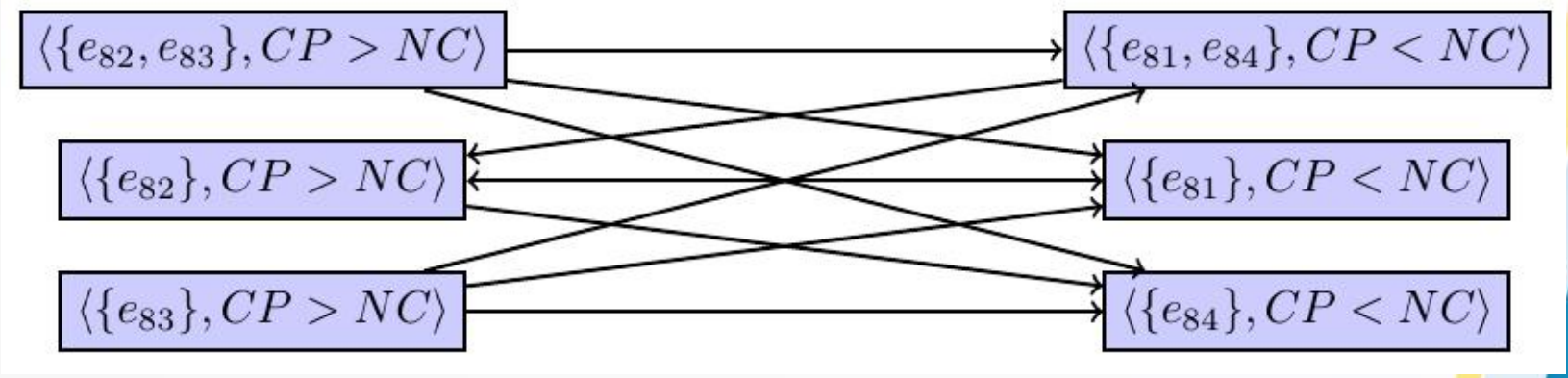


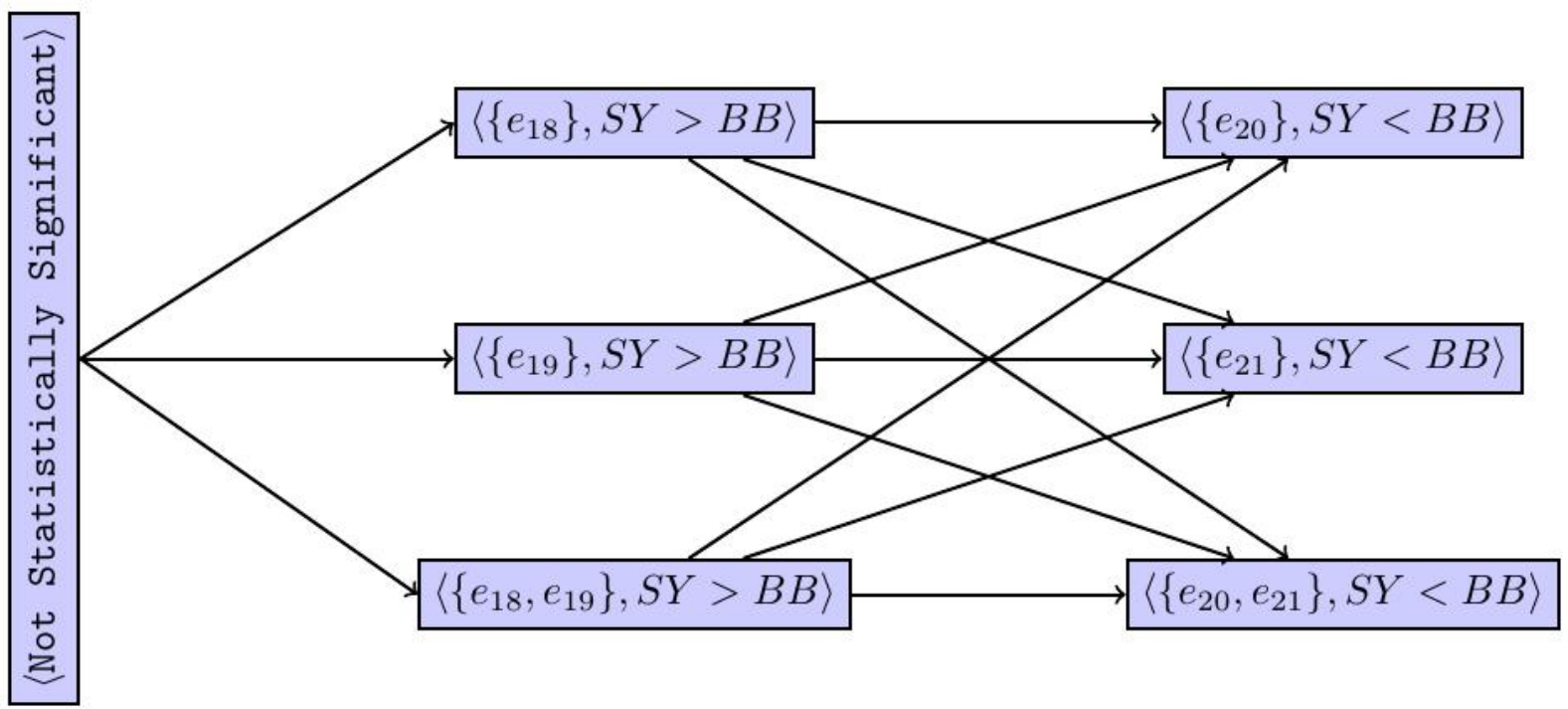
Meta-arguments

- Arguments against the quality of the evidence.
- They are atomic arguments (i.e. there is no internal structure to them).
- They are used as counterarguments to inductive arguments.
- Examples:
  - The evidence contains flawed RCTs.
  - The evidence contains results that are not statistically significant.
  - The evidence is from trials that are for a very narrow patient class.
  - The evidence has inconsistent outcomes.

Evidencial argument graph

- An evidential argument graph is a directed graph where:
  - each node is either an inductive argument or a meta-argument.
  - each arc is either an attack by a preferred inductive argument or an attack by a meta-argument.

Evidencial argument graph



Evidence Table

Where:

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e_{17}	CA	BB	hyperaemia	6.42	<	no	MA
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e_{20}	SY	BB	allergic prob	41.00	<	yes	MA
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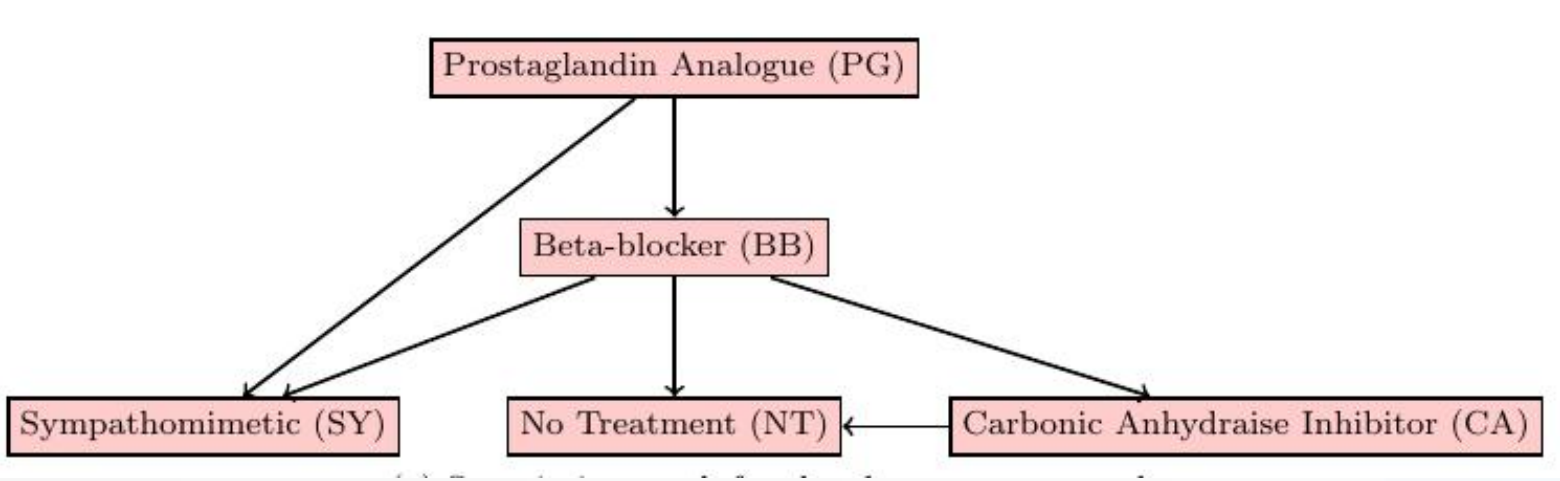
Each row is a meta-analysis from the NICE glaucoma GL for patients with raised IOP (i.e. at risk of glaucoma and thus, irreversible damage to the optic nerve and retina).

Evidence aggregation

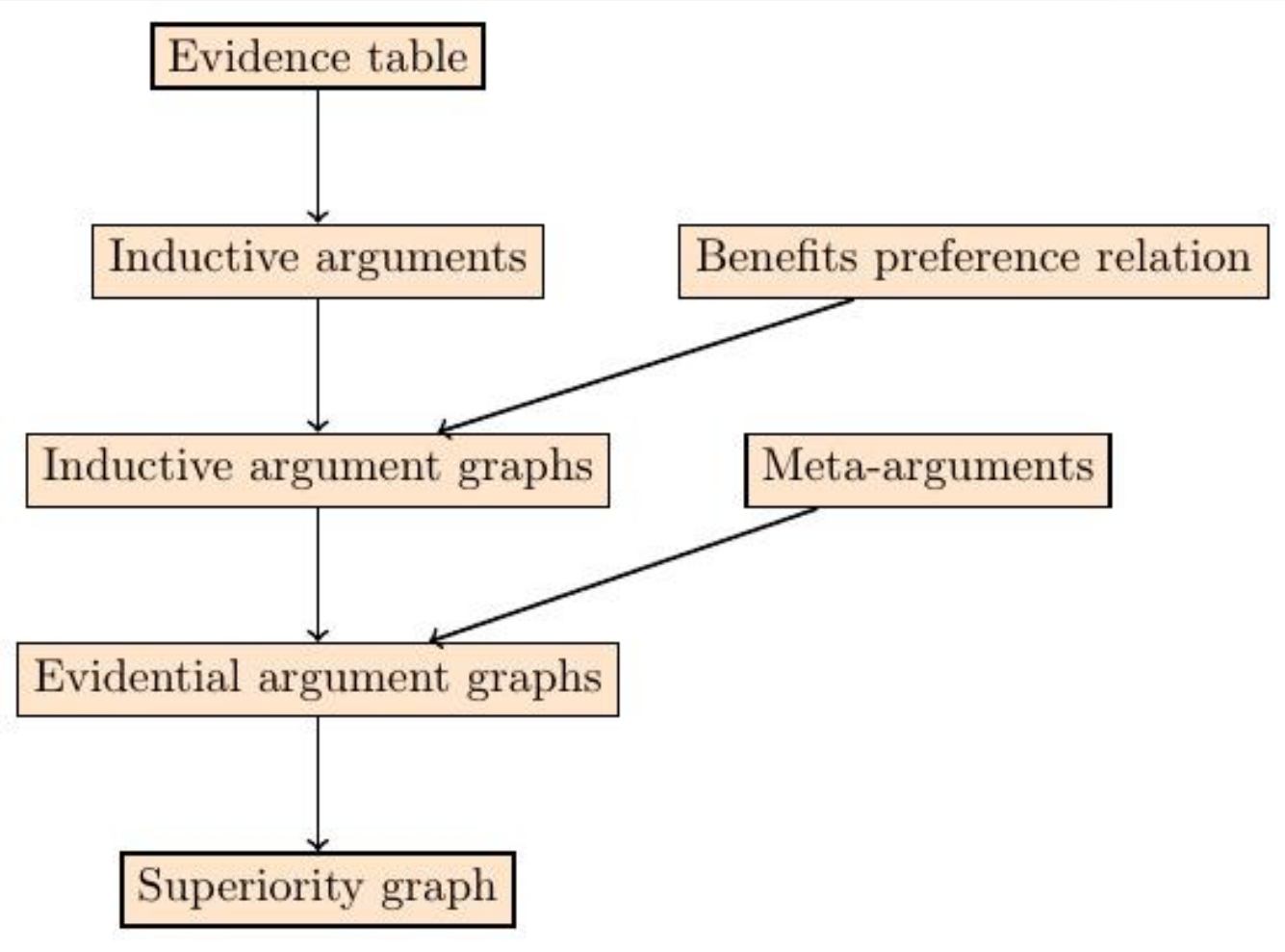
- If there is a non-empty grounded extension, and ϵ is the claim of the arguments in the extension, the result of the aggregation is ϵ.
- If there is an empty grounded extension, then there are multiple preferred extensions (e.g. E_1 , ..., E_n), so the result of the aggregation are ϵ_1, ... or ϵ_n, where ϵ_1 is the claim of the arguments in E_1 and ... and ϵ_n is the claim of the arguments in E_n.

Aggregation through argumentation



Result from the argumentation with the glaucoma case, where a directed arc from τ_1 to τ_2 denotes τ_1 is superior to τ_2 and an undirected arc from τ_1 to τ_2 denotes τ_2 is superior or equivalent or inferior to τ_2.

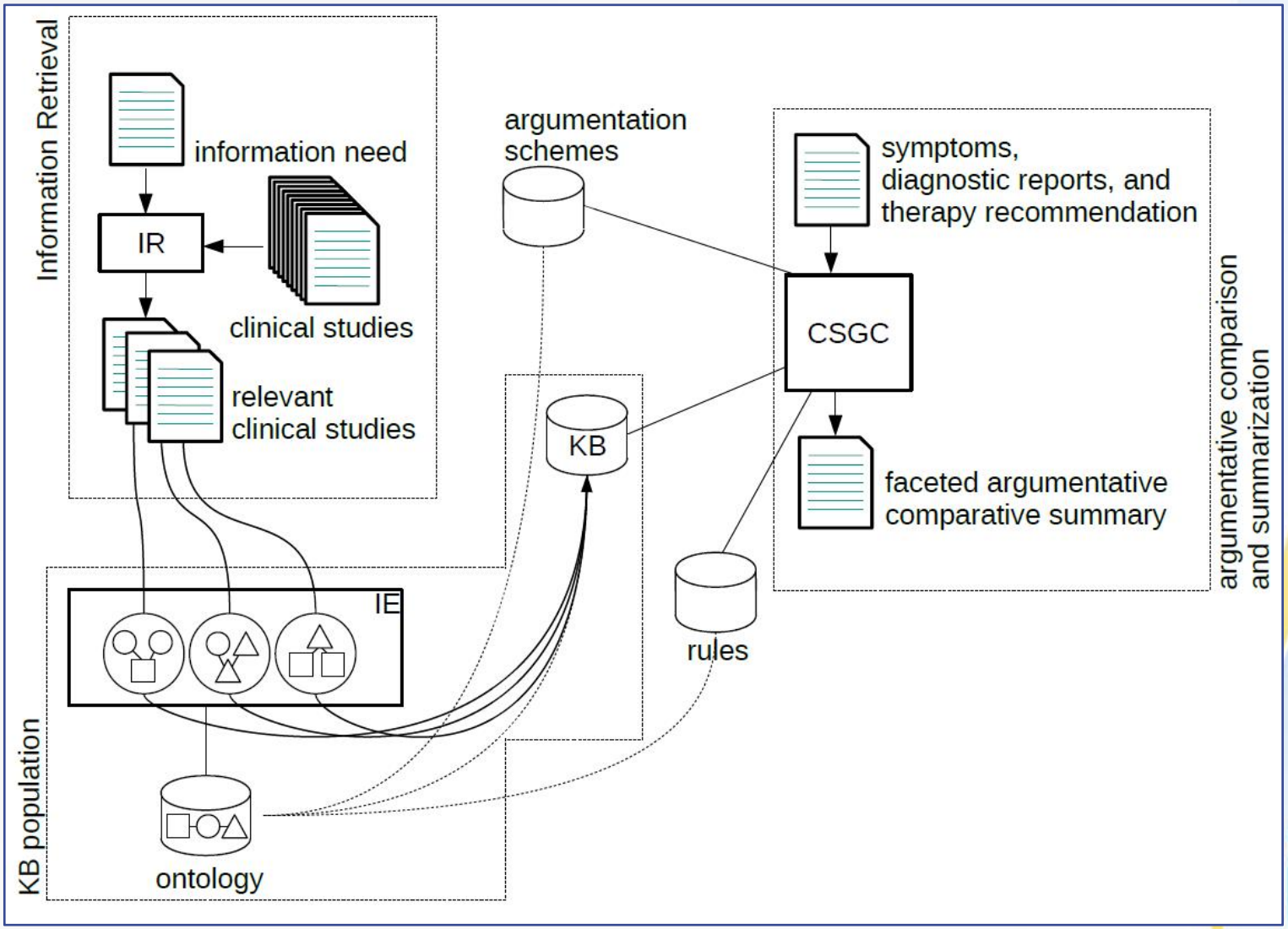
Summary of the approach for aggregation through argumentation



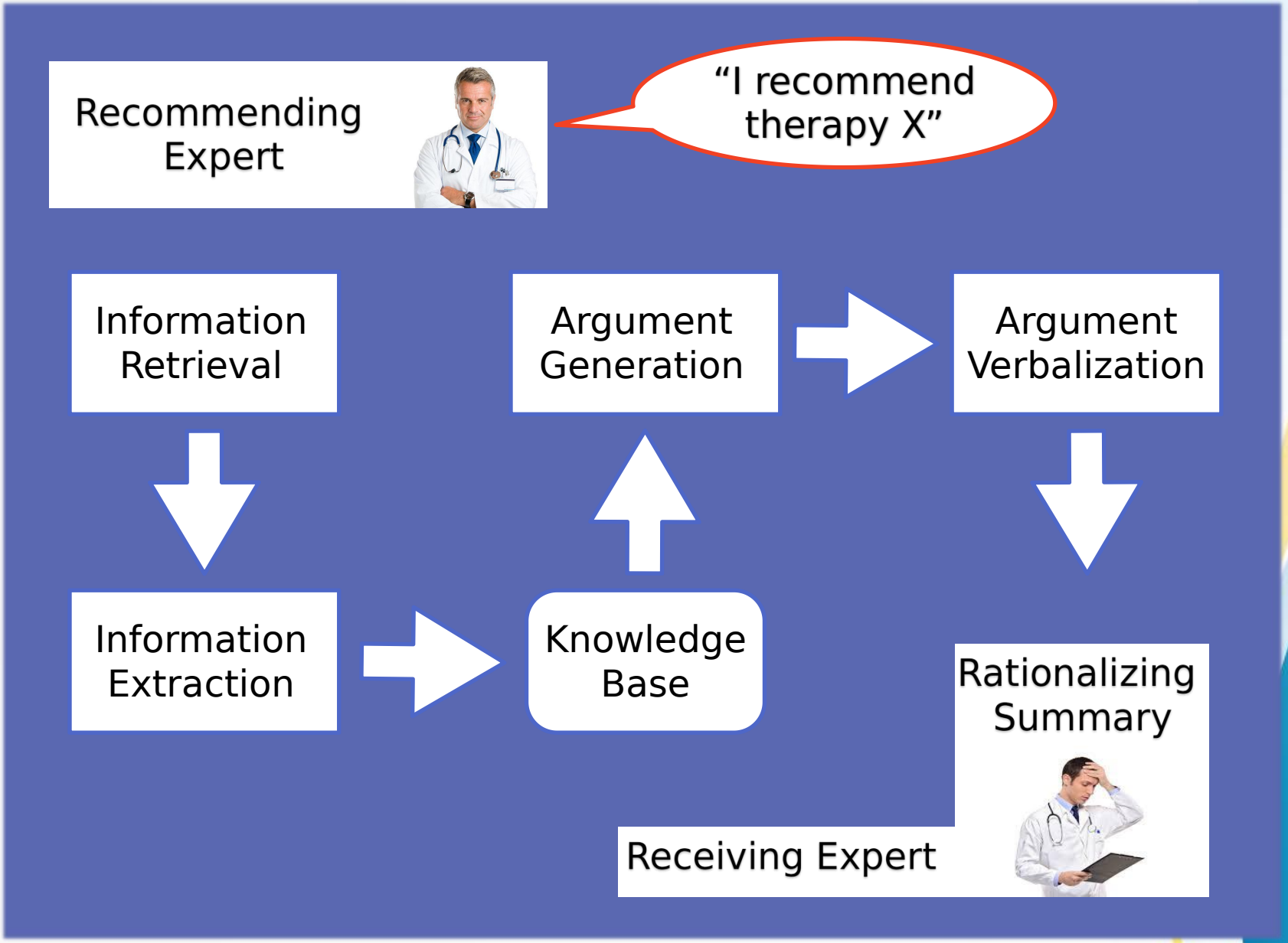
Part VI

Framework for rationalising clinical recommendations

Framework for rationalising clinical recommendations



Recommendations



The semantic model

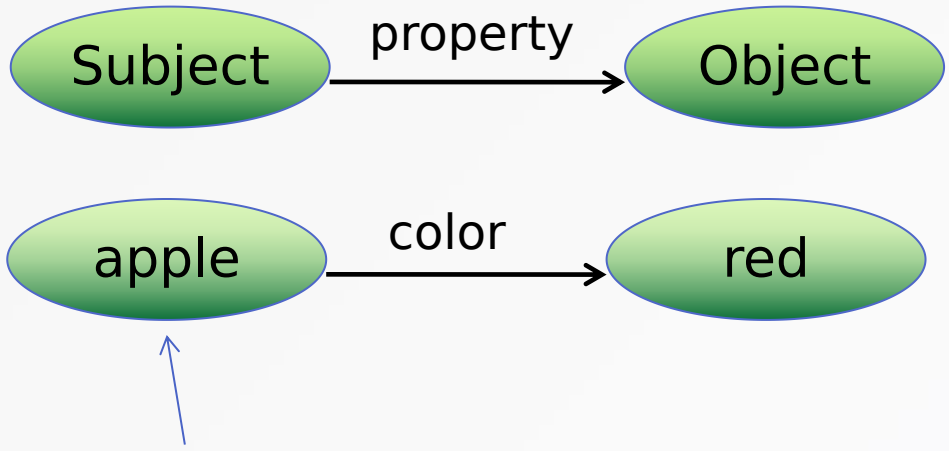
Database models

Model	Example format	Data	Metadata	Identifier	Query Syntax	Semantics (meaning)
Object Serialization	.NET CLR Object Serialization	Object Property Values	Object Property Names	e.g. Filename	LINQ	N/A
Relational	MS SQL, Oracle, MySQL	Table Cell Values	Table Column Definitions	Primary Key (Data Column) Value	SQL	N/A
Hierarchical	XML	Tag/Attribute Values	XSD/DTD	e.g. Unique Attribute Key Value	XPath	N/A
Graph	**RDF/XML, Turtle**	**RDF**	**RDFS/OWL**	**URI**	**SPARQL**	**Yes, using RDFS and OWL**

http://www.linkeddatatools.com/semantic-modeling

The Resource Description Framework (RDF)

- Framework for representing information in the Web
- Graph-based model for recording data that is internationally interchangable



URI (Uniform Resource Identifier)
http://www.linkeddata.com/fruits#apple

Semantic Web model

- This model allows sharing data from different sites across the web, by using:
  - Common *vocabulary*: terms given a well-defined meaning that is consistent across contexts.
  - *Ontology*: allows to define contextual relationships behind a defined vocabulary.
  - A formal syntax for defining ontologies such OWL (Web Ontology Language), which is an extension of RDFS (RDF Schema).

Web Ontology Language (OWL)

- Goal of ontology: classifying things in terms of semantics or meaning.
- OWL does this through classes, subclasses and instances (individuals).
- A class is a classification of individuals into groups which share common characteristics.
- An individual is under the semantic classification given by the corresponding class.

OWL properties

- Individuals are related by properties:
  - *Object* properties (owl:ObjectProperty) relates individuals (instances) of two classes.
  - *Datatype* properties (owl:DatatypeProperty) relates individuals (instances) of classes to literal values.

RDFS and OWL

- RDFS and OWL are the main syntaxes for annotating RDF data.
- RDFS and OWL are W3C specifications.

```
<?xml version="1.0"?>
<rdf:RDF xmlns="http://www.semanticweb.org/root/ontologies/2018/6/clitrial#"
     xml:base="http://www.semanticweb.org/root/ontologies/2018/6/clitrial"
     xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
     xmlns:owl="http://www.w3.org/2002/07/owl#"
     xmlns:xml="http://www.w3.org/XML/1998/namespace"
     xmlns:xsd="http://www.w3.org/2001/XMLSchema#"
     xmlns:rdfs="http://www.w3.org/2000/01/rdf-schema#"
     xmlns:clitrial="http://www.semanticweb.org/root/ontologies/2018/6/clitrial#">
    <owl:Ontology rdf:about="http://www.semanticweb.org/root/ontologies/2018/6/clitrial"/>

<!-- http://www.semanticweb.org/root/ontologies/2018/6/clitrial#CT10_Population -->

<owl:NamedIndividual rdf:about="http://www.semanticweb.org/root/ontologies/2018/6/clitrial#CT10_Population"/>


</rdf:RDF>
```

Why to use web ontologies?

- Knowledge integration across different domains in automatic way (use of URIs).
- No need for transformation, mapping, or contracts among different sites.
- Communications among sites through semantics.
- Query a semantic database (knowledge base).
- Perform machine inference on that knowledge base.

SPARQL

- Is a protocol and an RDF query language.
- SELECT: selects data from a dataset.
- FROM: indicates the site where the dataset to be queried is located.
- WHERE clause: defines graph patterns to find a match for it in the dataset.
- Graph pattern: consists of the subject, predicate and object triple.

SPARQL: General form

PREFIX (Namespace Prefixes)

```
e.g. PREFIX plant: <http://www.linkeddatatools.com/plants>
```

SELECT (Result Set)

```
e.g. SELECT ?name
```

FROM (Data Set)

```
e.g. FROM <http://www.linkeddatatools.com/plantsdata/plants.rdf>
```

WHERE (Query Triple Pattern)

```
e.g. WHERE { ?planttype plant:planttype ?name }
```

ORDER BY, DISTINCT etc (Modifiers)

```
e.g. ORDER BY ?name
```

The C-TrO Ontology for aggregation of clinical studies

C-TrO: main goals

- provide the structure for a KB that stores CT information and related information.
- provide the logical structure for summarising and aggregating evidence from multiple trials.
- support an annotation scheme of CT publications.

C-TrO: requirements

- Describe any type of clinical trial (e.g. randomized, crossover, parallel, etc.)
- Any health condition (e.g. disease, disorder, etc.)
- Consider important evidence for superiority of interventions:
  - risk of bias, results according to a given aggregation method
  - relative or absolute risk
  - size of effect of the interventions

PICO elements

P	I	C	O
Population / Problem	Intervention	Comparison	Outcome
What are the characteristics of the Population or Patient? What is the Problem, condition or disease of interest?	Which interventions are applied to the patients?	What is the Comparison or alternative to the intervention: placebo, a different drug, surgery, etc.?	What are the possible Outcomes of the study: reduce morbidity, death, complications, etc.?

P

- Patients with elevated intraocular pressure (IOP),male and female, mean age 61.9 years.

I

- latanoprost

C

- compared with timolol maleate

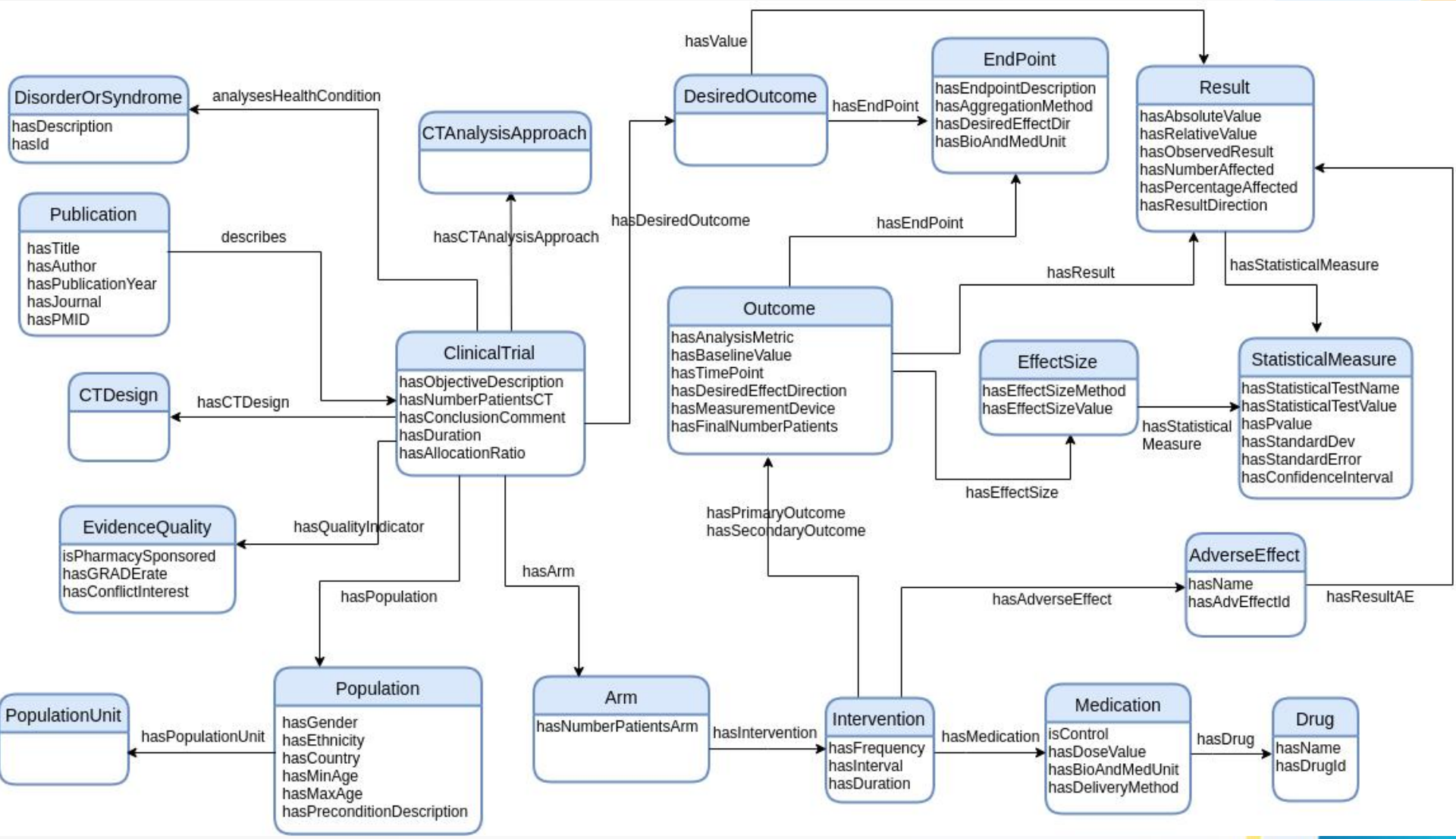
O

- effective in reducing mean diurnal (IOP)
- low rate in allergic response

Related CT ontologies

RCT Schema	PICO Ontology	OCRe	C-TrO
Preparation of reports and analysis of randomized clinical trials.	Annotation of Cochrane Reviews according to its PICO models.	Indexing of research data across different clinical data resources.	Knowledge base and annotation schema for the aggregation of the level of evidence of clinical trials.

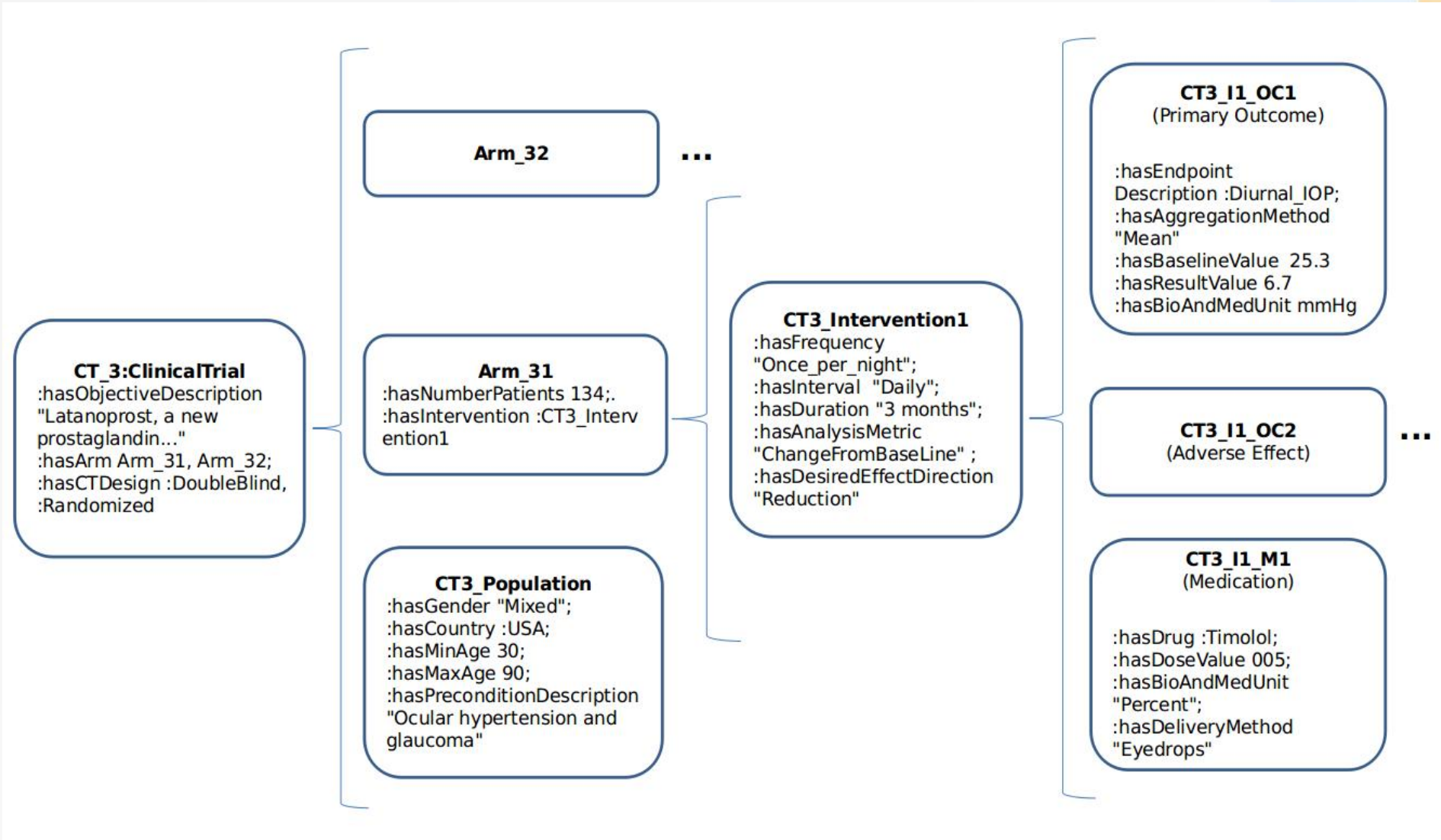
C-TrO


DisorderOrSyndrome
hasDescription
hasId
analysesHealthCondition
CTAnalysisApproach
DesiredOutcome
hasValue
hasEndPoint
EndPoint
hasEndpointDescription
hasAggregationMethod
hasDesiredEffectDir
hasBioAndMedUnit
Result
hasAbsoluteValue
hasRelativeValue
hasObservedResult
hasNumberAffected
hasPercentageAffected
hasResultDirection
Publication
hasTitle
hasAuthor
hasPublicationYear
hasJournal
hasPMID
describes
hasCTAnalysisApproach
hasDesiredOutcome
hasEndPoint
hasResult
hasStatisticalMeasure
Outcome
hasAnalysisMetric
hasBaselineValue
hasTimePoint
hasDesiredEffectDirection
hasMeasurementDevice
hasFinalNumberPatients
ClinicalTrial
hasObjectiveDescription
hasNumberPatientsCT
hasConclusionComment
hasDuration
hasAllocationRatio
EffectSize
hasEffectSizeMethod
hasEffectSizeValue
StatisticalMeasure
hasStatisticalTestName
hasStatisticalTestValue
hasPvalue
hasStandardDev
hasStandardError
hasConfidenceInterval
hasStatistical Measure
CTDesign
hasCTDesign
hasEffectSize
hasPrimaryOutcome
hasSecondaryOutcome
EvidenceQuality
isPharmacySponsored
hasGRADErate
hasConflictInterest
hasQualityIndicator
AdverseEffect
hasName
hasAdvEffectId
hasAdverseEffect
hasResultAE
hasPopulation
hasArm
Population
hasGender
hasEthnicity
hasCountry
hasMinAge
hasMaxAge
hasPreconditionDescription
Arm
hasNumberPatientsArm
PopulationUnit
hasPopulationUnit
hasIntervention
Intervention
hasFrequency
hasInterval
hasDuration
hasMedication
Medication
isControl
hasDoseValue
hasBioAndMedUnit
hasDeliveryMethod
hasDrug
Drug
hasName
hasDrugId

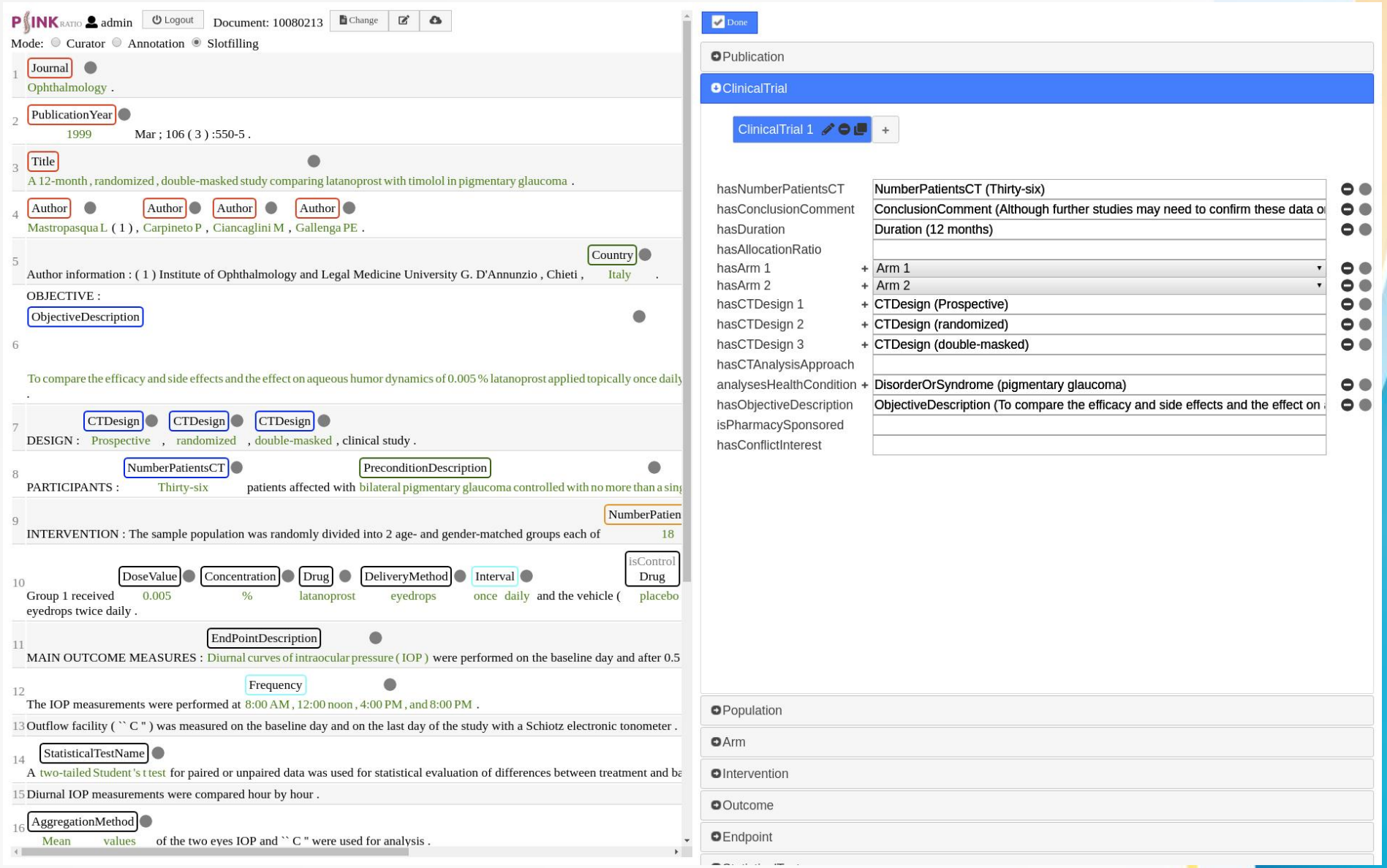
C-TrO: Knowledge base

:CT_3 rdf:type ctro:ClinicalTrial ;
:hasObjectiveDescription "Latanoprost, a new prostaglandin..." ;
:hasConclusionComment "Latanoprost has the potential..." ;
:hasAnalysisApproach PreProtocol ; :hasArm Arm_31, Arm_32 ;
:hasPopulation :CT3_Population ; :hasCTDesign :DoubleBlind, :Randomized .
:Arm_31 rdf:type ctro:Arm ;
:hasNumberPatients 134 ; :hasIntervention :CT3_Intervention1 .
:CT3_Population rdf:type ctro:Population ;
:hasGender "Mixed" ; :hasMinAge 30 ; :hasMaxAge 90 ; :hasCountry :USA ;
:hasPreconditionDescription "Ocular hypertension and glaucoma" .
:CT3_Intervention1 rdf:type ctro:Intervention ;
:hasFrequency "Once_at_evening"; :hasInterval "Daily" ;
:hasDuration "3 months"; :hasAnalysisMetric "ChangeFromBaseLine" ;
:hasDesiredEffectDirection "Reduction" :hasPrimaryOutcome :CT3_I1_OC1 ;
:hasAdverseEffect :CT3_I1_OC2 ; :hasMedication :CT3_I1_M1 .
:CT3_I1_OC3 rdf:type ctro:Outcome ;
:hasEndpoint :EndPoint_CT3_I1_OC3 ;
:hasAggregationMethod "Mean" ; :hasBaselineValue 25.3 ;
:hasBioAndMedUnit :mmHg ; :hasResult :Result_CT3_I1_OC3 .
:EndPoint_CT3_I1_OC3 rdf:type ctro:EndPoint ;
:hasEndpoint Description :Diurnal_IOP .
:Result_CT3_I1_OC3 rdf:type ctro:Result ;
:hasResultValue 6.7 .
:**CT3_I1_M1 rdf:type ctro:Medication;**
:hasDrug :Timolol; :hasDoseValue 005;
:hasBioAndMedUnit "Percent"; :hasDeliveryMethod "Eyedrops".

C-TrO: Knowledge base



Used for annotation of CTs



Used for annotation of CTs

#AnnotationID,ClassType,
DocCharOnset(incl),DocCharOffset(excl),Text,Meta,Instances
1,Journal,0,15,"Br J Ophthalmol", "", "<http://ctro/data/Publication_1>
<http://ratio.de/ctro/hasJournal>\"Br J Ophthalmol\"."
2,PublicationYear,18,22,"1994","","<http://ctro/data/Publication_1>
<http://ratio.de/ctro/hasPublicationYear>\"1994\"."
3,Title, 50,177,"Additive effect of latanoprost, a prostaglandin F2 alpha analogue , and timolol in patients with elevated intraocular pressure","","<http://ctro/data/Publication_1>
<http://ratio.de/ctro/hasTitle>\"Additive effect of latanoprost, a prostaglandin F2 alpha analogue , and timolol in patients with elevated intraocular pressure\"."
4,Author,180,187,"Rulo AH","","<http://ctro/data/Publication_1>
<http://ratio.de/ctro/hasAuthor>\"Rulo AH\"."
5,Author,196,204,"Greve EL","","<http://ctro/data/Publication_1>
<http://ratio.de/ctro/hasAuthor>\"Greve EL\"." ....
8,Country,289,304,"The Netherlands","",

RDF File
<http://ctro/data/Publication_1> <http://ctro/data/describes>
<http://ctro/data/ClinicalTrial_1> .

Argument Schemes for reasoning about evidence in clinical trials

AS for superiority in terms of efficacy

Major premise: For people who suffer a given disease/health-disorder, it is desirable that a certain outcome indicator (or measurement) related to that disease/health-disorder changes, that is either increasing or decreasing.
Minor premise: It has been shown in a number of comparable clinical trials that $T1$ changes (either increasing or decreasing) a given disease/health-disorder indicator from the baseline in terms of an aggregation method in greater magnitude than $T2$.
Conclusion: $T1$ is a more effective medication treatment compared to $T2$ for changing the given disease/health-disorder indicator in the desired direction.

Critical Questions:
CQ1: Is the change (either increasing or decreasing) of the given disease/health-disorder indicator statistically significant (p-value)?
CQ2: Is the size of effect of $T1$ bigger than the one of $T2$?
CQ3: Are $T1$ and $T2$ applied to a comparable number of patients across the different studies?

AS for superiority in terms of safety

Major premise: For people who suffer a given disease/health-disorder and who are under a medication treatment, it is desirable not to suffer any adverse effect.
Minor premise: It has been shown in a number of comparable clinical trials that administration of $T1$ leads to less incidence of adverse effects compared to the administration of $T2$.
Conclusion: Therefore, $T1$ is superior to $T2$ in terms of its safety profile.

Critical Questions:
CQ1: Is the adverse effect statistical significant?
CQ2: Is the size of effect of the adverse effect bigger for $T2$ than for $T1$?

Critical Questions

CQ3: How reliable and trustable is the evidence from these studies?

- ***CQ3.1*** Is there a risk of bias?
- ***CQ3.2*** Is the study randomized?
- ***CQ3.3*** Is the study blind?
- ***CQ3.4*** Is the study multi-center?
- ***CQ3.5*** Is the study intention-to-treat?

Use case of glaucoma: efficacy

Major premise: For people who suffer glaucoma it is desirable that the *diurnal mean IOP* is reduced.
Minor premise: It has been shown in eleven comparable clinical trials that *latanoprost* treatments reduced the *diurnal mean IOP* from baseline in greater magnitude than *timolol* treatments.

Evidence			
CT_Id	**Reference**	**Mean IOP reduction by Latanoprost (mmHg)**	**Mean IOP reduction by Timolol (mmHg)**
CT_1	Alm A et al,1995	7.8	6.7
CT_1	Alm A et al,1995	8.6	6.7
CT_10	Nicolela MT et al.,1996	6.8	5.3
CT_11	Drance SM et al.,1998	3.6	3.1
CT_2	Aquino MV et al.,1999	11.1	9.1
CT_3	Camras CB et al.,1996	6.7	4.9
CT_4	Diestelhorst M et al.,1998	4.9	2.1
CT_5	Mastropasqua L et al,1999	4.8	4.6
CT_6	Mishima HK et al.,1996	6.2	4.4
CT_7	Rulo AH et al.,1994	8.9	5.9
CT_8	Watson P et al,1996	8.5	8.3
CT_9	Diestelhorst M et al.,1997	9.8	6.7

Conclusion: *latanoprost* treatment is a more effective medication treatment compared to *timolol* treatment for reducing the diurnal mean IOP.

Use case of glaucoma: efficacy

CQ1: Is the reduction of the diurnal mean IOP statistically significant?

CT_Id	**Intervention_Id**	*p*-**value**	**Intervention_Id**	*p*-**value**
CT_1		N/A		N/A
CT_1		N/A		N/A
CT_10		N/A		N/A
CT_11		N/A		N/A
CT_3	CT3_Intervention1	< 0.001	CT3_Intervention2	< 0.001
CT_2	CT2_Intervention1	< 0.001	CT2_Intervention2	< 0.001
CT_3		N/A		N/A
CT_4		N/A		N/A
CT_5	CT5_Intervention1	< 0.001	CT5_Intervention2	< 0.001
CT_6		N/A		N/A
CT_7		N/A		N/A
CT_8		N/A		N/A
CT_9	CT9_Intervention1	< 0.001	CT9_Intervention2	< 0.001

Use case of glaucoma: safety

Major premise: For people who suffer glaucoma and who are under a medication treatment it is desirable not to suffer any adverse effect.
Minor premise: It has been shown in eleven comparable clinical trials that the administration of the *timolol* treatment leads to less incidence of *Conjunctival_hyperemia* than the *latanoprost* treatment.

Evidence			
Latanoprost		**Timolol**	
Adverse effect	**Number**	**Adverse effect**	**Number**
IncreasedPigmentation	2	IncreasedAqueousHumorProtein	1
IrisPigmentationChange	1	ChangeBloodVelocity	1
Conjunctival_hyperemia	**7**	ReducedHeartRate	2
		ReducedBloodPreasure	2
		Smarting	1
		IrisPigmentationChange	1
		Conjunctival_hyperemia	**2**

Conclusion: The *timolol* treatment is superior to the *latanoprost* treatment in terms of its safety profile, leading to less cases of the adverse effect *Conjunctival_hyperemia*.

CQ1: Is the presence of *Conjunctival_hyperemia* statistically significant?

No statistical significance was reported for this adverse effect.

Glaucoma case: Critical Questions

CQ3.1 Is there a risk of bias? *No risk of bias was reported for any clinical study.*
CQ3.2 Is the study randomized?
CQ3.3 Is the study blind?
CQ3.4 Is the study a multi-center?
CQ3.5 Is the study an intention-to-treat? *None study was a ITT-study.*

Evidence for CQ3.2, CQ3.3, CQ3.4	
CT_Id	**Design**
CT_1	Randomized Crossover Multicenter DoubleMasked
CT_10	Crossover DoubleMasked
CT_11	Randomized DoubleMasked
CT_2	Parallel Randomized DoubleMasked SingleCenter
CT_3	Parallel Randomized Multicenter DoubleMasked
CT_4	Parallel Randomized Multicenter DoubleMasked
CT_5	Randomized DoubleMasked
CT_6	Parallel Randomized DoubleMasked
CT_7	Parallel Masked Randomized
CT_8	Randomized DoubleMasked
CT_9	Randomized DoubleMasked

Instantiation via SPARQL

```
SELECT DISTINCT ?ct ?reference ?reduction1 ?reduction2
WHERE{
{
{SELECT ?d1 ?d2
WHERE{?d1 rdf:type :Drug.
?d2 rdf:type :Drug. filter(?d1 != ?d2)} limit 1}
?medic1 :hasDrug ?d1.
?medic2 :hasDrug ?d2.
?interv1 :hasMedication ?medic1.  ?interv2 :hasMedication ?medic2.
?interv1 :hasPrimaryOutcome ?outcome1.
?interv2 :hasPrimaryOutcome ?outcome2.
?outcome1 :hasEndPoint ?endpoint1. ?outcome2 :hasEndPoint ?endpoint2.
?endpoint1 :hasEndpointDescription :Diurnal_IOP.
?endpoint2 :hasEndpointDescription :Diurnal_IOP.
?endpoint1 :hasResultValue ?result1.  ?endpoint2 :hasResultValue ?result2.
bind(str(?result1) as ?reduction1)  bind(str(?result2) as ?reduction2)
?arm1 :hasIntervention ?interv1.  ?arm2 :hasIntervention ?interv2.
?ct :hasArm ?arm1. ?ct :hasArm ?arm2.
?pub :describes ?ct. ?pub rdfs:label ?reference.
FILTER (?result1 > ?result2)
```

Thanks!