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Biomarkers Working Group Fall Dinner Session

Marina Del Ray

Oct. 1, 2012

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Agenda

- Review Biomarker Working Group (BWG) origins and mission statement
- Review of BWG activities to date
- Qualitative review and meta analysis for imaging in schizophrenia clinical trials focused on neuroimaging changes associated with drug treatment
- Explore existing methodologies to increase efficiency in biomarker selection from Paul Song and Jerry Borak from Dr. Evidence
- Review the complex interplay between neuroimaging and genetic biomarkers in schizophrenia by Dr. Steven Potkin
- Discussion of next steps for BWG

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Origins of BWG

- As CNS drug development advances toward an increasingly personalized approach to treatment, the role of various biomarkers has become ever more important for informing clinicians about the relative safety, tolerability and efficacy of a range of CNS drugs and products.
- In addition, biomarkers can aid in the development of novel therapeutic agents, identify susceptible populations, provide endpoints for clinical trials and even serve as predictor variables.
- The growing interest in biomarkers raises many challenges for diverse stakeholders regarding both the structure and elements of clinical trials that are needed to establish valid scientific data in support of these biomarkers

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Origins of BWG

- Unfortunately, CNS drug developers currently lack sufficient data and many of the tools necessary to successfully implement the use of biomarkers in the drug development process
- Given this, and the burden of development and qualification of biomarkers in terms of both time and cost, the formation of collaborative international groups to undertake these biomarker related challenges is essential.
- These challenges also provide a unique opportunity for meaningful industry-academia-government collaboration; and the Biomarkers Working Group (BWG) is being formed to help meet these challenges while ensuring that the interests and expertise of the International Society for CNS Clinical Trials and Methodology are both thoughtfully considered and communicated to the Society's members

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Origins of BWG

- Developing Products for Personalized Medicine: Facing the Challenges of Biomarkers
- Chairs: Karl Broich, MD / Larry Alphs, MD, PhD 23 February 2011
- Outcome of Meeting
  - Deeper understanding of how biomarkers can be used in CNS development
  - Insights into the viewpoints of different stakeholders
  - Practical experience in addressing development of biomarkers
  - Innovative ideas that move this research forward in CNS field
  - A way forward towards CNS personalized medicine
  - Better more directed treatments for CNS patients
  - **Formation of ISCTM working group**

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BWG Mission Statement

- Formally review and respond to current and future FDA or EMEA guidance on biomarkers and their opinion's regarding qualifying biomarkers.
  - For example, the EMEA recently released its first Qualification Opinion of Alzheimer's Disease Novel Methodologies/biomarkers for BMS-708163 for public opinion, and a formal review and response by the ISCTM BWG may be beneficial.
  - Deliverable: summary review supplied to appropriate agency and white paper or review article for publication if and when applicable

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BWG Mission Statement

- As biomarkers are submitted and become approved by the FDA/EMEA the BWG will track and supply an inventory of all qualified biomarkers that can be applied across various CNS drug development programs as a reference for IND submission potentially eliminating the need for submitting extensive biomarker-supportive information with each IND.
  - Deliverable: a spreadsheet posted on ISCTM website tracking the progress of all biomarkers in the qualification process as well as their use in any regulatory submissions that is updated quarterly

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BWG Mission Statement

- Review and critique the literature on the utility of various biomarkers across multiple pediatric and adult CNS indications, that may include schizophrenia, bipolar disorder, depression, Alzheimer's disease, MS, stroke, analgesia as well as other indications.
- This review will be spearheaded by those ISCTM members with relevant expertise bringing in outside expertise as needed, and result in formal ongoing presentations at one of the two ISCTM conferences each year.
- It is expected that there will be an in depth review of at least one indication or therapeutic area per year.

  - Deliverable: a one hour biomarkers session each year at an ISCTM conference and posting a white paper on the ISCTM website and/or a related publication.
  - Each deliverable will be overseen by the BWG chairs and lead by unique contributors.

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Biomarkers in Clinical Trials

Oct 3, 2011 Fall Meeting Amelia Island FLA

Imaging for Schizophrenia: Issues in identification, categorization and evaluation

Workshop Chairs:
Nathan Chen and Susan De Santi

Biomarker Working Group Chairs:
Hank Riordan and Steve Potkin

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Fall Meeting FLA

- Introduction: History of the biomarkers working group (Larry Alphs)
- Goal & Objectives (Susan De Santi)
  - Imaging: practical – ahead in the literature, background of workshop committee
- Methodology of Approach to Assessing literature (Nathan Chen)
- Discussion of Imaging Technique
  - Volumetric MRI (Susan De Santi and Hank Riordan)
  - DTI (Christine Moore)
  - FMRI (Theo Van Erp)
  - FDG-PET (Dan van Kammen)
  - Receptor PET and SPECT (Nathan Chen and Dong-Jing Fu)
- Summary and next steps
- ISCTM website link for viewing articles:
  - http://isctm.org/Imaging_Biomarkers_in_Schizophrenia_Lit_Review

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Annual Meeting DC

- Provided a summary of the *qualitative* grading data for imaging biomarkers (sMRI, fMRI, DTI, FDG/receptor PET & SPECT) suggesting highest rating for sMRI.
- Reviewed the *quantitative* data and meta analytic procedures for sMRI changes in various ROIs associated with treatment effects with largest ES for white matter decreases over time.
- Introduced the process and services offered by Dr. Evidence that could potentially be utilized by the BWG in future activities.
  - A formal presentation by Dr. Evidence on replication of meta analyses at the Fall 2012 meeting is anticipated.
- Explored the possibility of registering schizophrenia imaging biomarkers meta analysis on Cochrane Collaboration as well as approach to publication supporting the utility of key biomarkers (cognition, ERP, imaging etc.) in a proof of concept setting.

A Qualitative Evaluation on Evidence Level for Selective Imaging Biomarkers in Schizophrenia Clinical Trials

Nathan Chen, MD PhD[1] ; Susan De Santi, PhD[2]; Dong Jing Fu, MD PhD[3] ; Daniel van Kammen, MD PhD[4]; Christine Moore, PhD[5] ;Theo van Erp, PhD[6] ; Henry Riordan, PhD[7] ; Steven Potkin, MD[8]

ISCTM Working Group for Workshop of Imaging Biomarker in Schizophrenia**

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Introduction:

The main objective of this qualitative evaluation was to provide a review of the utility of imaging biomarkers in schizophrenia as a measure of treatment response. Schizophrenia treatment studies that included the structural or functional imaging modalities, including vMRI, fMRI, FDG-PET, receptor occupancy PET & SPECT, and DTI were identified, categorized, and evaluated. We report on the results of this qualitative evaluation for these putative imaging biomarkers.

Methods:

Human clinical trials, published after 1995, on the selected imaging biomarkers

- Databases Isearched included PsycInfo, MEDLINE, PubMed, and Google Scholar.
- Standardized Information template* including type of imaging biomarker, trial design, intervention, patient population characteristics, and major efficacy findings for image region of interest (ROI) as well as tolerability assessment.
- Qualitative evidentiary standard evaluation using grading of evidence level outlined by Altar et al's (2008) (Table 1).
- Evidence matrix for 1) theory of biological plausibility, 2) interaction with pharmacologic target, 3) pharmacologic mechanistic response, 4) linkage to clinical outcome of a disease, 5) mathematic replication confirmation, 6) analytic validation, and 7) relative performance.

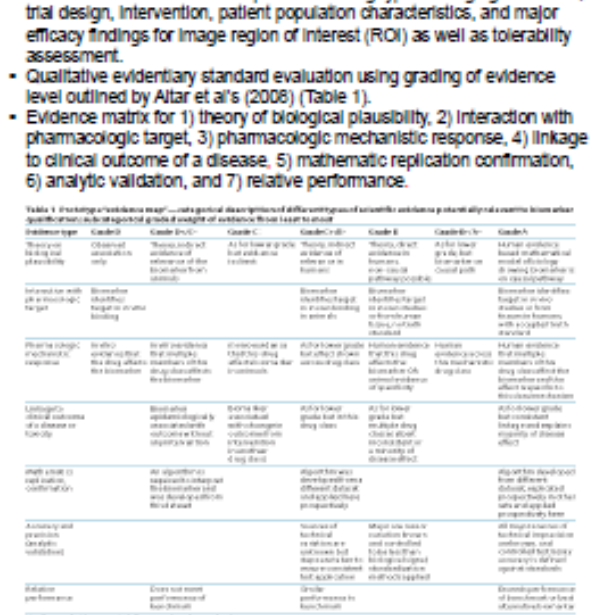

Table from Altar CA, Amakey D, Bounos D, et al (2008) A prototypical process for creating evidentiary standards for biomarkers and diagnostics. Clinical Pharmacology and Therapeutics, 83 (2): 368-371

**Author-Affiliations:

1 Clinical Sciences, PCMU, Pfizer Inc, Groton, CT;
2 GW Healthcare, Princeton, NJ & Department of Psychiatry, NYU Langone Medical Center, New York, NY;
3 Janssen Scientific Affairs, Titusville, NJ, USA;
4 CNS Pharma Consulting, LLC;
5 PharmaNeeds, Cary NC;
6 Department of Psychiatry & Human Behavior, School of Medicine, University of California Irvine, Irvine, CA;
7 Medical & Scientific Affairs, Worldwide Clinical Trials;
8 Department of Psychiatry & Human Behavior, University of California, Irvine, CA

Results:

850 articles met the predetermined criteria. 81 articles were reviewed. Evidence grading varied with imaging biomarkers, ranging from A- for receptor occupancy measured by PET or SPECT to D- for DTI with various supporting reasons for grading. Summary of key findings and potential gaps are listed in table 2.

Table 2: Summary of key findings, gaps and evidence level for each modality of the selected imaging biomarkers

	Paper Identified	Abstract Reviewed	Articles on Target	Key Findings	Gaps	Evidence Level
vMRI	265	100	35	▪ Volume loss of frontal grey matter in schizophrenia at various stage ▪ Loss of both grey and white matter vs treatment by typical antipsychotics ▪ Loss of grey matter but increase of white matter vs treatment by atypical antipsychotics	▪ Large long term study ▪ Consistent methods for imaging acquisition and analysis	A-
fMRI	1881	15+	15	▪ Evidence for psychopharmacological effects on cerebral physiology (e.g., percent signal change in frontal lobe regions). ▪ Evidence for psychopharmacological effects on functional connectivity	▪ Large long term study ▪ PET-fMRI combination	B
DTI	250	16	10	▪ No prospective study prospectively examined between group treatment effects ▪ Anisotropy in pts generally lower than healthy controls; lower still in pts with "poor outcomes ▪ Anisotropy reductions in pts take place earlier in the course of illness, closer to the time of first psychotic episode and stabilize in its chronic phase, but inconsistent findings and confounded by age and illness duration.	▪ Prospective study with between group analysis	D
FDG-PET	7	7	7	▪ Resting rCBF was significantly lower in schizophrenia compared to normal controls ▪ Schizophrenics has significantly higher right and left contrast enhancement compared to normal controls ▪ Antipsychotics was associated with greater change toward normal values & away from the values found in the unmedicated comparison group for dorsolateral prefrontal cortex grey matter and white matter underlying medial prefrontal and cingulate cortex.	▪ Correlation with treatment response ▪ Long-term prospective study	C+ - B-
PET	184	40	22	▪ Model to characterized dose –occupancy relationship ▪ Striatal D2/D3 occupancy predicted both improvement of positive symptoms and occurrence of EPS	▪ Long-term prospective study with between group analysis	B+ - A-
SPECT	50	25+	25	▪ See PET ▪ Limited 5HT2A blockade in antipsychotic action ▪ Confirm neurotransmitter dysfunction of D2, 5-HT2A, NMDA, GABA, muscarinic receptors ▪ Regional Cerebral Blood Flow (rCBF) analysis suggested hypofrontality ▪ Evidence of differential rCBF related to antipsychotic efficacy and cognitive improvements	▪ Comparison with other platforms ▪ Long-term prospective study	B* - A-

Receptor Occupancy – PET*

Review process for PET D2/D3 occupancy is presented to illustrate the qualitative evaluation for each modality

Database: MEDLINE, Google Scholar, PubMed

Major Key Words: Receptor Occupancy, PET, Schizophrenia, Clinical Response

- 104 papers identified:
- 40 abstracts selected and reviewed
- 22 total "on target", including 1 meta-analysis and 2 review articles

Required information collected according to the Standard Information Template*

PET scan methodology:

- Standardized scan protocol and sequence
- Ligand varied by antipsychotics or receptor type, for instance[11C]raclopride for D2/D3 receptor, [18F]setoperone for 5HT2 receptor.
- BL PET scans at pre-dose, follow up scans at steady state of plasma concentration and performed 12-15 hours after last dose.

Patient population:

- Drug free (naïve, wash-out) first-episode schizophrenia patients
- Clinic setting or hospitalized patients
- Efficacy measured by PANSS and CGI, EPS measured by various scales, hyperprolactinemia defined by plasma level.

Key Findings:

- Established model to characterize relationship between plasma concentration/dose and striatal D2/D3 receptor occupancy
- Striatal D2 receptor occupancy related to both efficacy and EPS, while no clear correlation of cortical D2/D3 occupancy with efficacy
- Striatal receptor occupancy predicted clinical improvement of antipsychotic treatment in schizophrenia
- 60-70% of striatal D2 occupancy is threshold of clinical responder
  - Quantitative model was established to characterize average striatal D2 occupancy and symptom improvement measured by PANSS
  - Significant correlation between PANSS positive symptom improvement and striatal D2 occupancy
  - Linear correlation between clinically effective dose and dose inducing maximal striatal D2/D3 receptor occupancy
  - No study prospectively examined between group treatment effects

Evidence Map:

- Good model to demonstrate drug's CNS penetration and action on targeted receptor
- Model to characterize dose-striatal D2/D3 relationship is well established and replicated in various drugs of both 1st or 2nd generation antipsychotics.
- Striatal receptor occupancy may predict clinical improvement of antipsychotic treatment, however, no established algorithm to explain the relationship or to apply this relationship to other data set prospectively .
- Evidence level was determined as B+ - A-

Gaps: need long-term prospective studies with between group analysis

Conclusion:

- Different imaging biomarker modalities are required at the various phases of clinical development of schizophrenia treatment.
- Matching the imaging modality to the research question should result in better utilization of imaging biomarkers in clinical research that are more sensitive to treatment effects in a clinical trial setting.
- Consistent method for imaging acquisition and analysis in each imaging modality is warranted

Reference:

Altar CA, Amakey D, Bounos D, et al (2008) A prototypical process for creating evidentiary standards for biomarkers and diagnostics. Clinical Pharmacology and Therapeutics, 83 (2): 368-371

*Addendum provided at presentation, including 1) Standard Information Template and 2) List of reviewed articles related to PET

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Summary Qualitative Grading of Evidence

	Paper Identified	Abstract Reviewed	Articles on Target	Key Findings	Gaps	Evidence Level
vMRI	265	100	35	• Volume loss of frontal grey matter in schizophrenia at various stage • Loss of both grey and while matter vs treatment by typical antipsychotics • Loss of grey matter but increase of while matter vs treatment by atypical antipsychotics	• Large long term study • Consistent methods for imaging acquisition and analysis	A^-
fMRI	1881	15+	15	• Evidence for psychopharmacological effects on cerebral physiology (e.g., percent signal change in frontal lobe regions). • Evidence for psychopharmacological effects on functional connectivity	• Large long term study • PET-fMRI combination	B
DTI	250	16	10	• No prospective study prospectively examined between group treatment effects • Anisotrophy in pts generally lower than healthy controls; lower still in pts with "poor outcomes • Anisotrophy reductions in pts take place earlier in the course of illness, closer to the time of first psychotic episode and stabilize in its chronic phase, but inconsistent findings and confounded by age and illness duration.	• Prospective study with between group analysis	D
FDG-PET	7	7	7	• Resting rCBF was significantly lower in schizophrenia compared to normal controls • Schizophrenics has significantly higher right and left contrast enhancement compared to normal controls • Antipsychotics was associated with greater change toward normal values & away from the values found in the unmedicated comparison group for dorsolateral prefrontal cortex gray matter and white matter underlying medial prefrontal and cingulate cortex.	• Correlation with treatment response • Long-term prospective study	C^+ - B^-
PET	184	40	22	• Model to characterized dose –occupancy relationship • Striatal D2/D3 occupancy predicted both improvement of positive symptoms and occurrence of EPS	• Long-term prospective study with between group analysis	B^+ - A^-
SPET	50	25+	25	• See PET • Limited 5HT2A blockade in antipsychotic action • Confirm neurotransmitter dysfunction of D2, 5-HT2A, NMDA, GABA, muscarinic receptors • Regional Cerebral Blood Flow (rCBF) analysis suggested hypofrontality • Evidence of differential rCBF related to antipsychotic efficacy and cognitive improvements	• Comparison with other platform • Long-term prospective study	B^+ - A^-

Meta-Analysis of Structural Magnetic Resonance Imaging (sMRI) Biomarkers In Schizophrenia Medication Trials

Henry J. Riordan, Ph.D[1]., Kathy Dawson, Ph.D[1]., Neal Cutler, MD[1]., Chwen-Cheng Nathan Chen, MD., Ph.D[2]., Steven Potkin[3], MD., and Susan DeSanti, Ph.D[4].
[1]Worldwide Clinical Trials, King of Prussia, PA and Beverly Hills, CA ; [2]Pfizer Inc, Groton, CT; [3]UC Irvine, Irvine, CA; [4]GE Healthcare Princeton, NJ

Abstract

Background: In order to determine the quality of evidence to support the application of imaging biomarkers in clinical trials of schizophrenia relevant sMRI literature was reviewed. A prior qualitative review following criteria by Altar et al (2008) suggested an evidence rating of "A-/B+" for sMRI in relation to medication effects. In order to provide a more quantitative evaluation a meta-analysis was undertaken to examine approved antipsychotic medication trials with at least one pre and post sMRI assessment.

Methods: A structured search of the literature utilizing PsycInfo, MEDLINE, PubMed, and Google Scholar databases yielded 265 papers for initial appraisal. Of these 100 abstracts were selected for more in depth review and of these 35 were reviewed more thoroughly. Careful examination revealed that ten publications were suitable for meta-analytic review containing adequate data to calculate effect sizes (ESs). Brain regions examined included whole brain, lobar volumes, basal ganglia and ventricular volumes, as well as grey and white matter. Subject numbers for individual studies ranged from 10 to 73 with 145 schizophrenic subjects included overall. To control for differences in sample size, studies were weighted according to their inverse variance estimates. Weighted ESs (Hedges g) were calculated for change from baseline for each brain region along with 95% confidence intervals.

Results: Analysis of intervention effects (d) on brain volume (across different types medication) revealed a moderate but non-significant overall effect size (g=0.452, 95% CI= -0.56, 0.17)). An analysis of homogeneity including all studies revealed no significant variance among effect sizes that would support examining the effects of moderator variables (Q_E[133]=133.299 12, p<0.45). Significant decreases associated with treatment were noted for a total white matter volume that was independent of study duration. This decrease was associated with typical but not atypical antipsychotic medications as a class and with two individual medications. An increase in grey matter was observed with one typical antipsychotic.

Discussion: While these initial results do not fully support the qualitative evidence grading they do suggest that it is possible to more confidently select specific brain regions that are more likely to be sensitive to antipsychotic medication effects. Further work is needed relating these ESs to changes in schizophrenia symptoms and outcomes.

Methods

•Studies were identified through a search of the MEDLINE, PsychINFO, PubMed and Google Scholar databases. Key words: brain volume, MRI, Schizophrenia, treatment response, efficacy, English, human

•Approximately 265 papers identified; abstracts reviewed 100 abstracts selected and reviewed. 35 papers were reviewed for this presentation including 1 meta-analysis and 4 review articles.

Methods (cont.)

Of these 10 yielded sufficient data on means and variance from which reliable ESs could be generated

•Information collected included:

- Scan protocols and sequences
  - T1 weighted SPGR (1.5T, 3T), Inversion Recovery, dual spin echo (CPMG)
- Patient population
  - Drug naïve and drug treated first-episode schizophrenics (FES) chronic schizophrenics
  - Treatments: Both typical and atypical antipsychotics
- Study designs
  - Cross sectional comparisons
  - Longitudinal studies: 4 weeks to 104 weeks

▪Overall, 12 ROIs were identified including whole brain, total grey matter, total white matter, ventricular size, various cortical lobes and subcortical structures. Number of observations for each ROI ranged from a low of 2 to a high of 80 (for grey matter). Whenever possible, specific regions of interest were grouped into structural areas such as basal ganglia (caudate nucleus, putamen, nucleus, accumbens).

▪ Analyses were conducted using Comprehensive Meta-Analysis, Version 2.0. In order to standardize medication effects a Hedge's g was utilized by calculating the mean difference in pre/post brain volume after pharmacologic treatment in schizophrenic patients and dividing this value by the pooled standard deviation with an adjustment for small sample bias.

▪In order to assess homogeneity across studies a Cochran Q-statistic was utilized. A random effects model was used to calculate effect sizes if the Q-statistic revealed significant within-group heterogeneity. In cases where significant heterogeneity was not indicated, fixed effects models were used.

Results

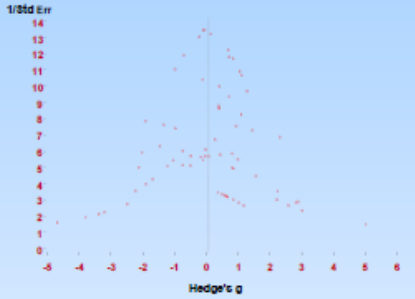
▪Analysis of intervention effects (g) on brain volume (across different types of medication) revealed a moderate overall effect size (g=0.45197, 95% CI= -.56, 0.17) according to Cohen criteria. Since 0 is included in the confidence interval it is not possible to conclude that the effect size is non-zero.

▪ An analysis of homogeneity including all studies revealed non-significant variance among study effect sizes that do not support examining the effects of moderator variables nor use of a random effects model (Q_E[133]=133.299 12, p<0.45.

Results (cont.)

▪ No evidence of publication bias was observed, as indicated by a symmetric funnel plot and confirmed by non-significant Begg and Egger tests (p>.05).

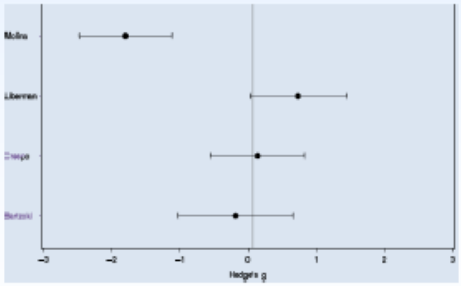
Funnel Plot for Publication Bias



▪Of the 12 ROIs only the total white matter effect yielded a significant effect size (g = -.57, CI -1.1 to -.01) related to decrease white matter volume associated with overall treatment.

▪ESs grew in response to study duration with the largest ES seen for studies >24 weeks duration (-0.56; -0.76; -0.94 for studies >4, 12 and 24 weeks, respectively. Of note, the overall ES is driven by the large delta seen in a single study as seen in the below forest plot.

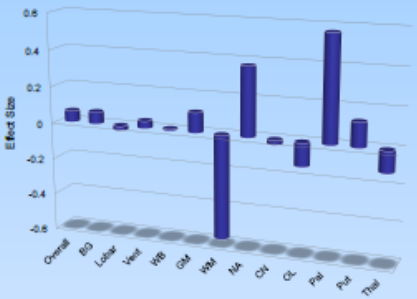
Forest Plot for White Matter ES



▪ Following is a graphic displaying the ESs associated with overall treatment for each brain region. Of note was an increase in volumes for the nucleus accumbens and the globus pallidus.

Results (cont.)

ES for Various Brain Volumes



Overall Effects suggested a decrease in overall white matter volume that was associated with treatment independent of study duration and type of drug. This ES grew with study duration being greatest for 24 week studies.

Class of Drug : As a class typical antipsychotic mediations were associated with decreases in white matter (g=-1.34) whereas no reliable changes were noted for atypical antipsychotics as a class (g=-0.35) as the CIs crossed zero.

Individual Drugs: Risperidone was associated with an overall decrease in white matter (g= -0.68) but an increase in grey matter. (g=0.24) Clozaril showed a similar pattern with larger ESs for both white matter. (g=-3.26) and grey matter (g=1.99).

Conclusions

▪Notwithstanding the possible backdrop of progressive brain deterioration and the limited data available to date, this preliminary meta analysis is amongst the first to report significant changes in brain volumes (white and grey matter total) associated with antipsychotic medication treatment.

▪The changes in WM over time are not unexpected but it is unclear if medication exacerbates these changes. Longitudinal Diffusion Tensor Imaging (DTI) studies may be helpful in elucidating this. The finding of increased grey matter volumes with certain drugs was somewhat surprising.

▪Although these ESs do not fully support the qualitative grading of evidence for sMRI it is clear that specific brain based biomarkers may have some utility in future efficacy and safety trials.

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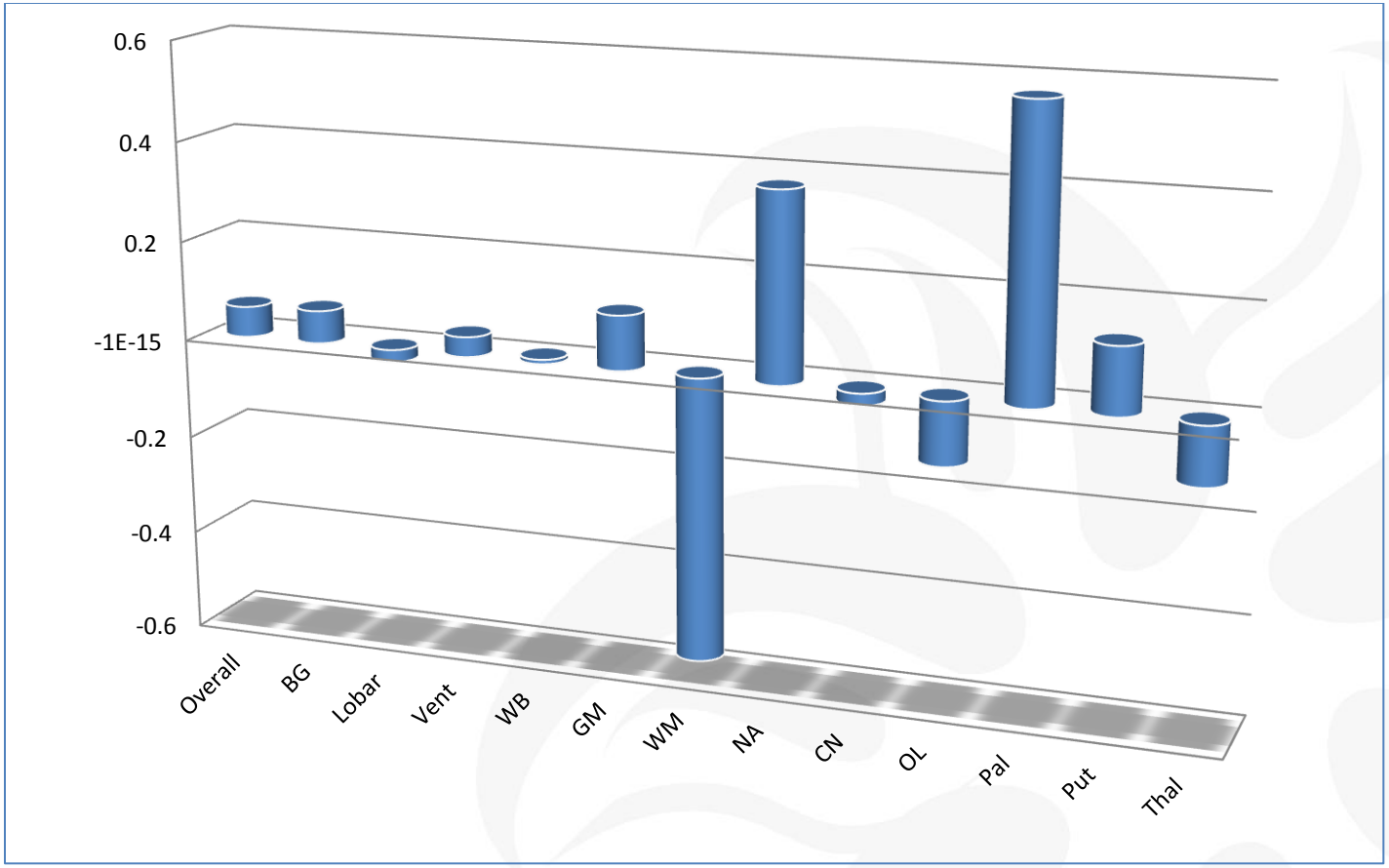
Summary sMRI Meta Analysis



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Doctor Evidence

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Doctor Evidence

- Founded in 2002
- Mission is to improve clinical outcomes by finding, delivering, and making relevant and readable medical evidence that enables clinicians to support informed decisions
- Clients include leading healthcare providers, payers, academic institutions & manufacturers
- Distinctive competencies are integrating leading EBM methodologies into one unified technology platform

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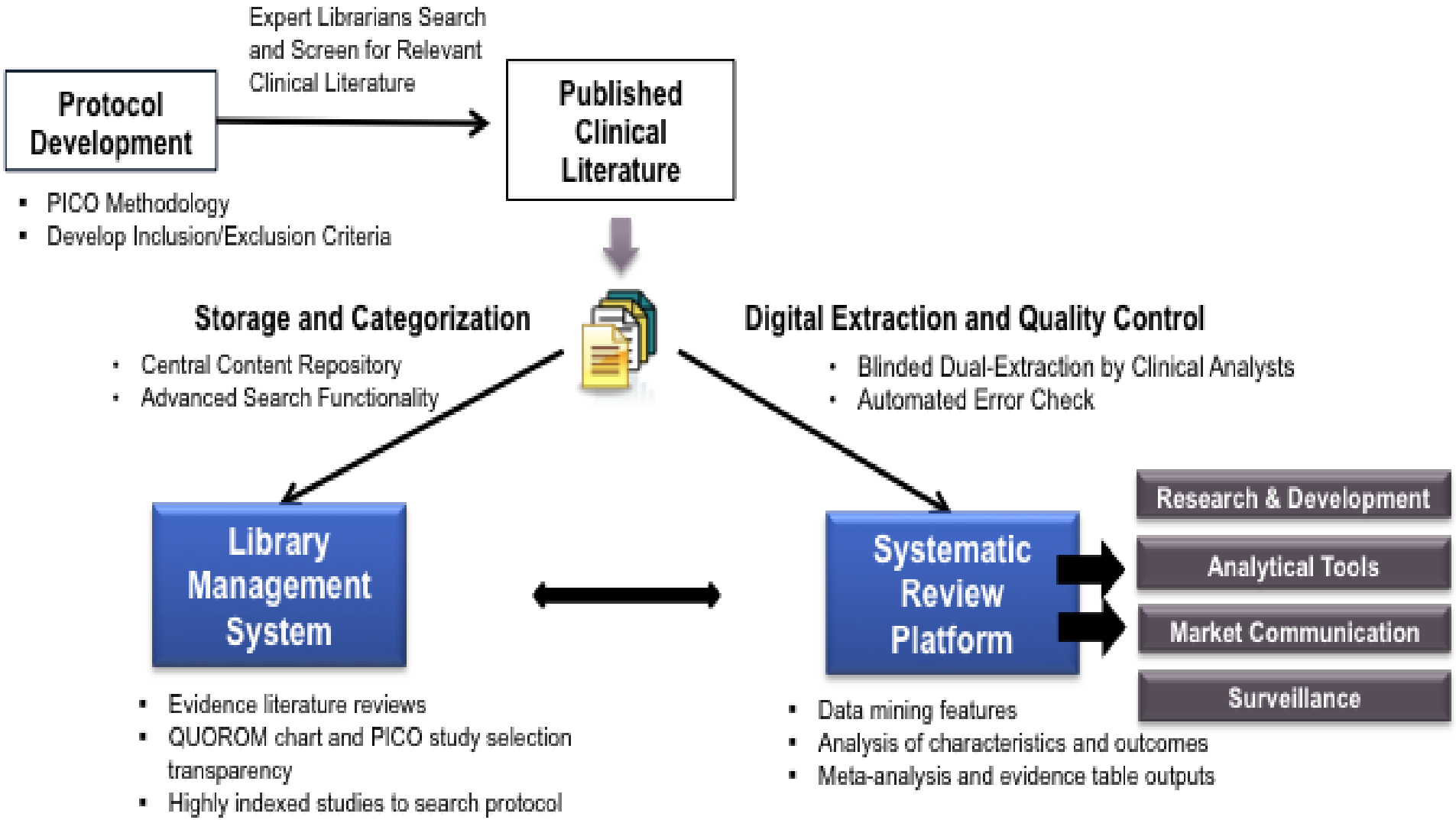
Doctor Evidence Process



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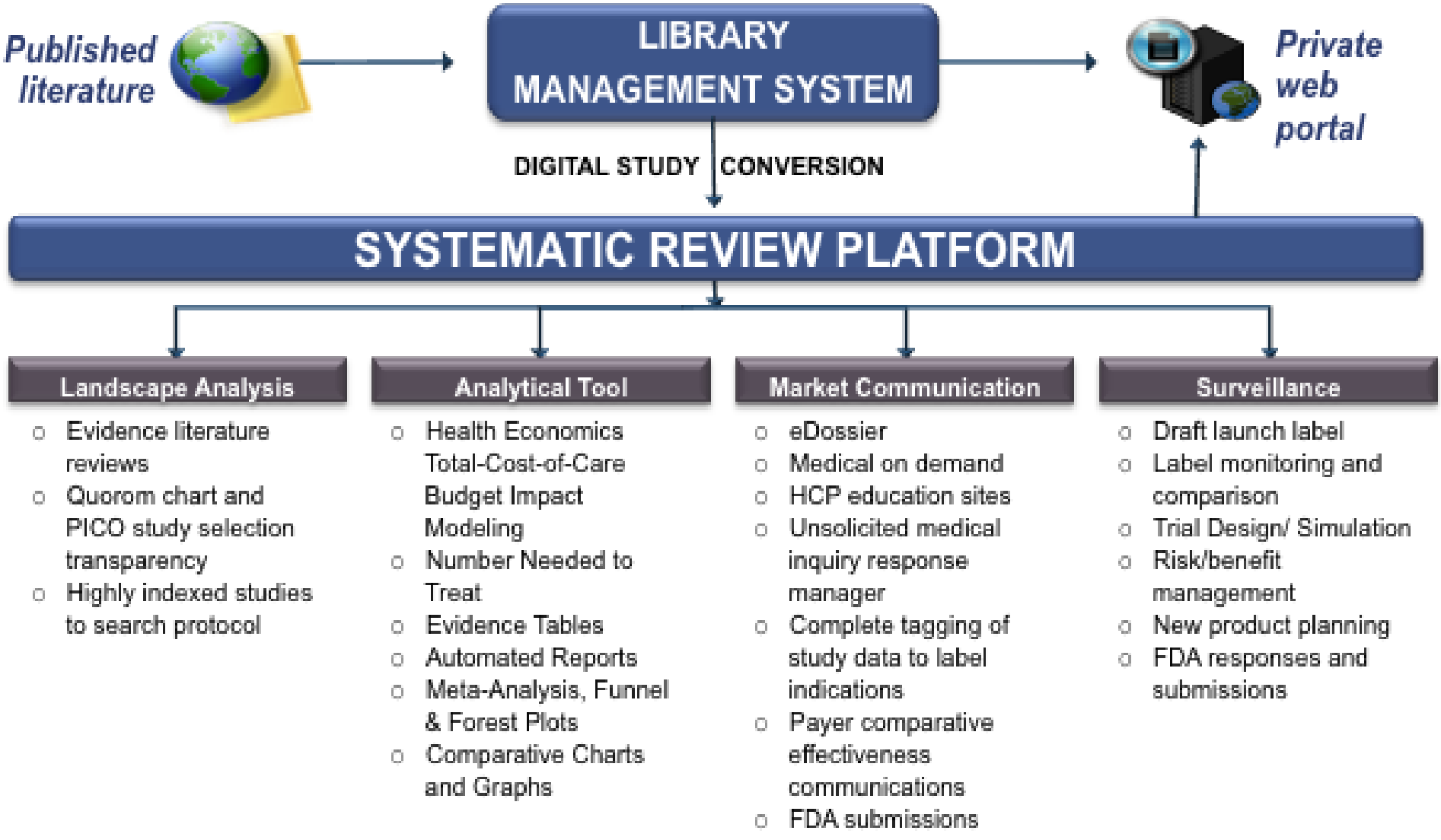
Doctor Evidence Comprehensive Systematic Review Platform



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Protocol Template

Portal and Database Protocol

1. What is/are the framed questions you would like to answer?

Note: As an adjunct to search and to help identify relevant articles, please provide Doctor Evidence with a list of references of clinical studies that should be reviewed during the database creation process.

Sample Framed Question

"What is the evidence regarding a sirolimus eluting stent compared with paclitaxel eluting stents or with bare metal stents in people with acute ST elevation myocardial infarction?"

2. What is the PICO, where P = patient population, I = intervention, C = comparison group, O = outcomes? *Note whether outcomes are "and/or".*

P =	
I =	
C =	
O =	

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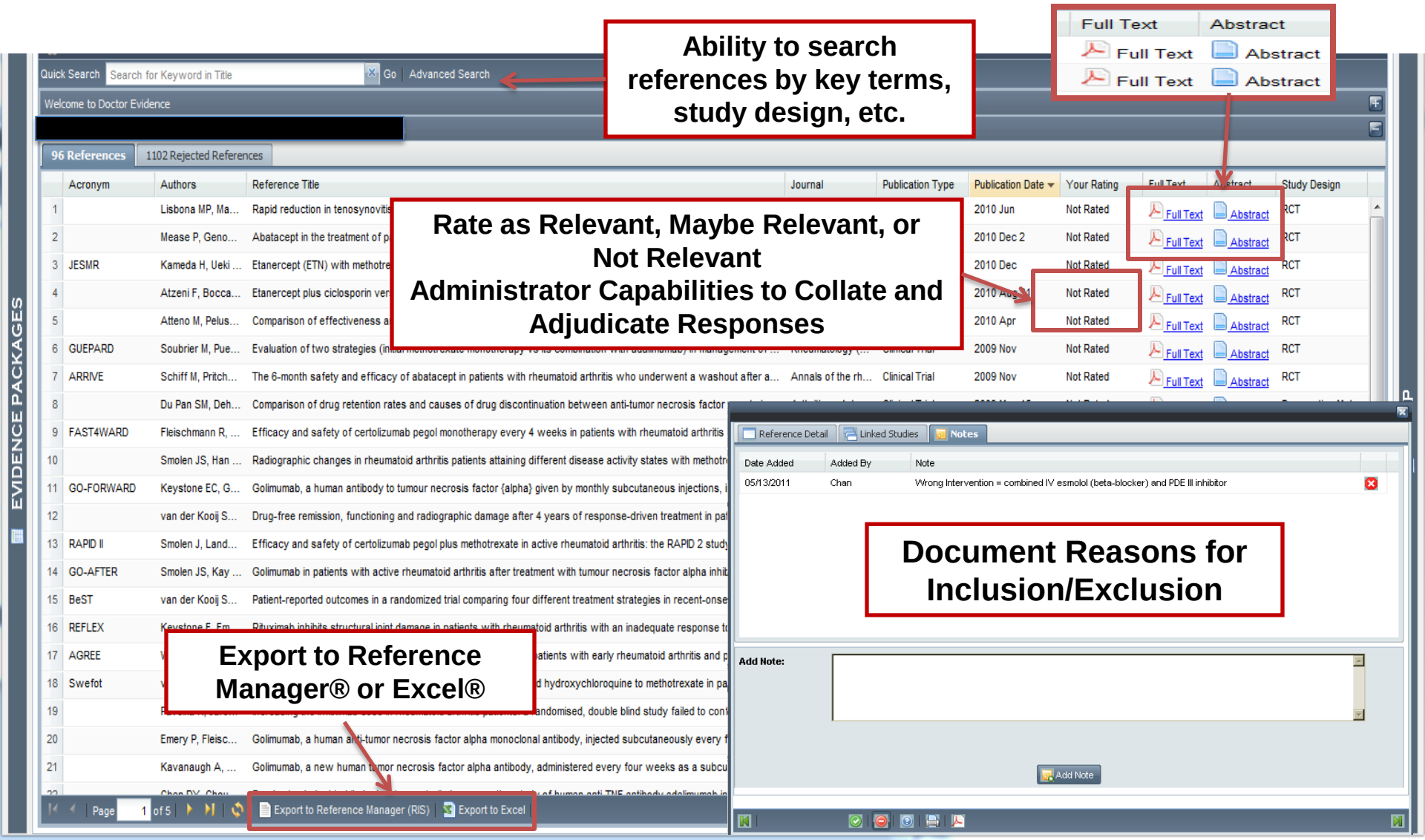
Library Management System



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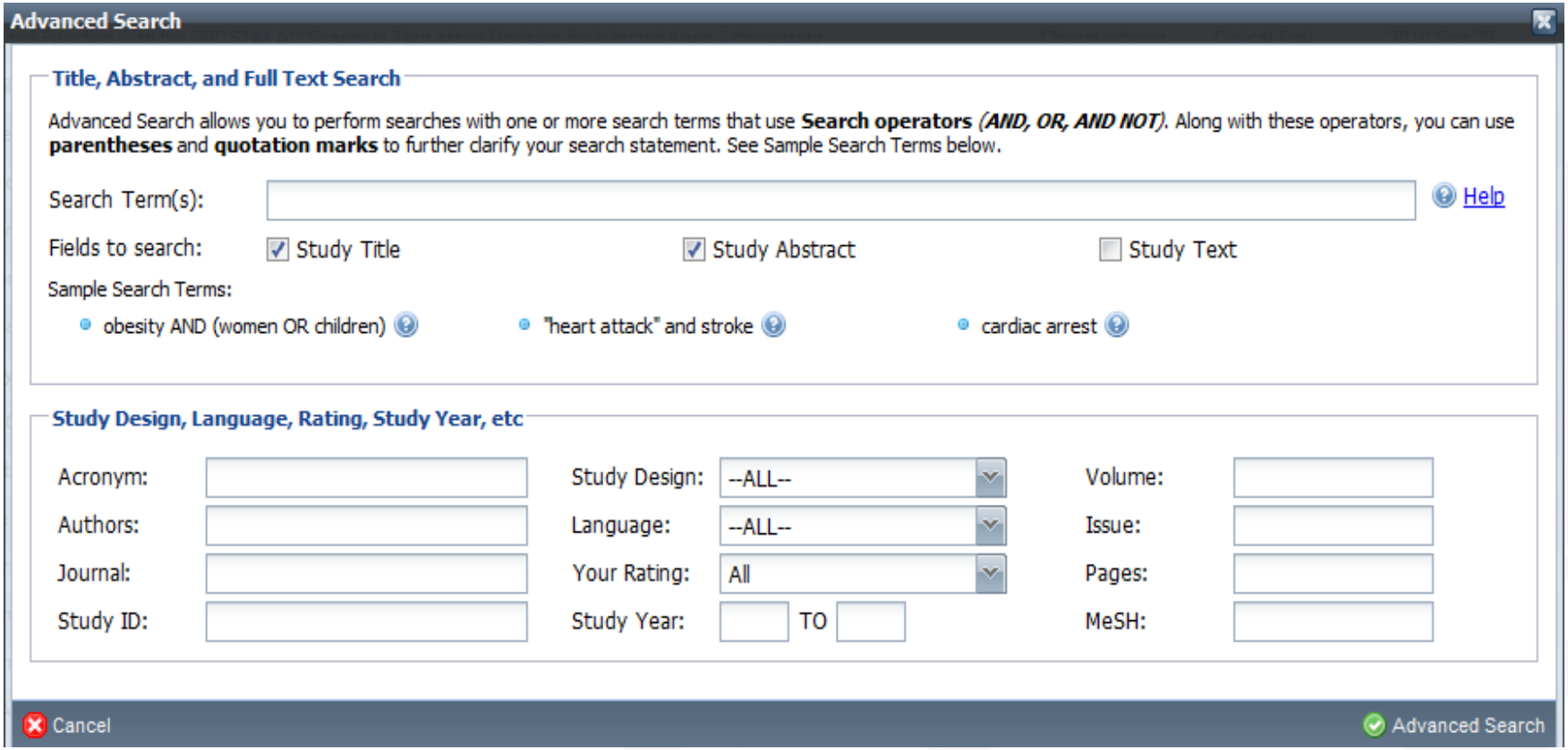
Advanced Search



Advanced Search, a robust search engine where users can search by key terms in the full text, abstract or title. Additionally, users can search by Study Design, Study Year, Journal, etc.

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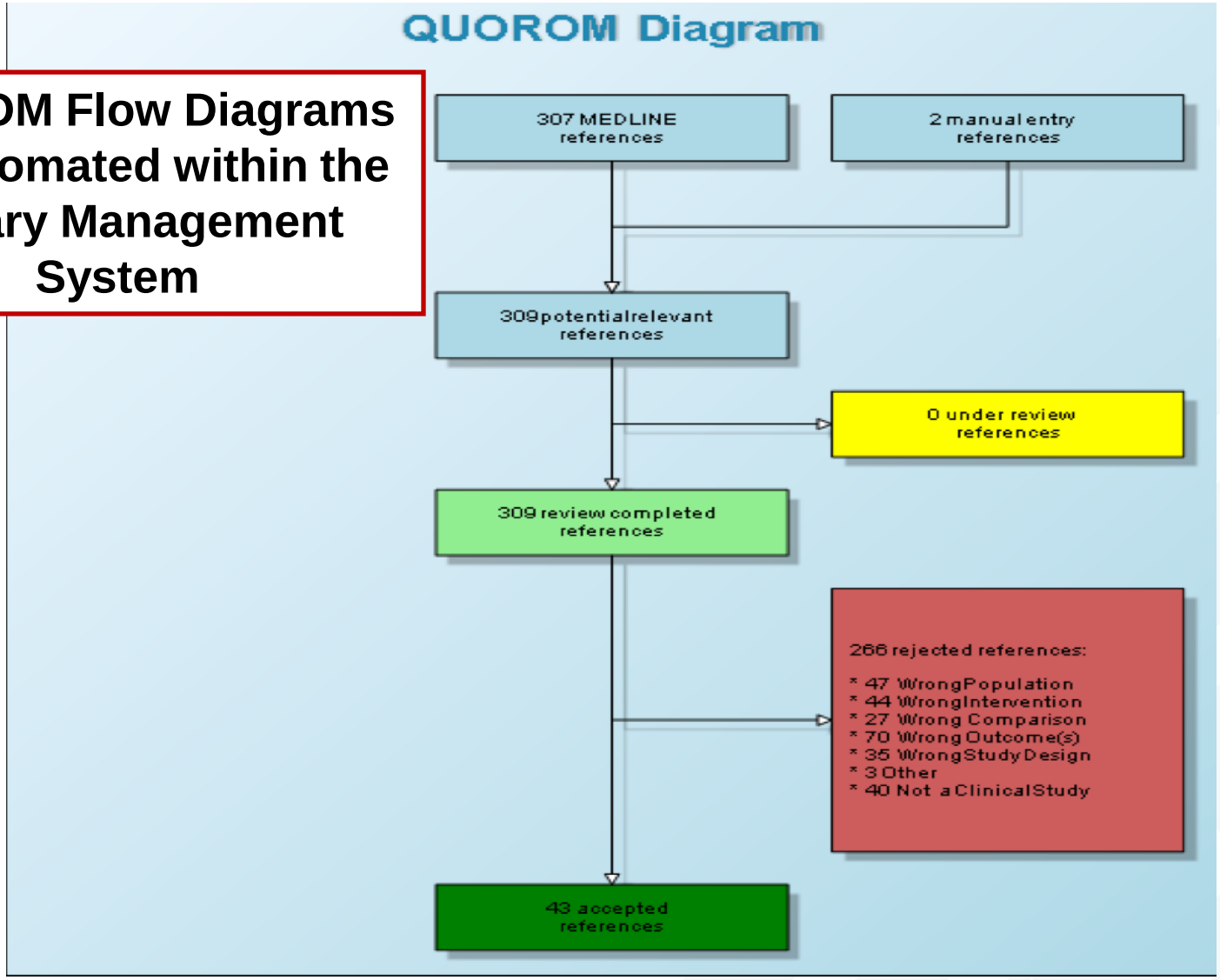
QUOROM Flow Chart

QUOROM Flow Diagrams are automated within the Library Management System



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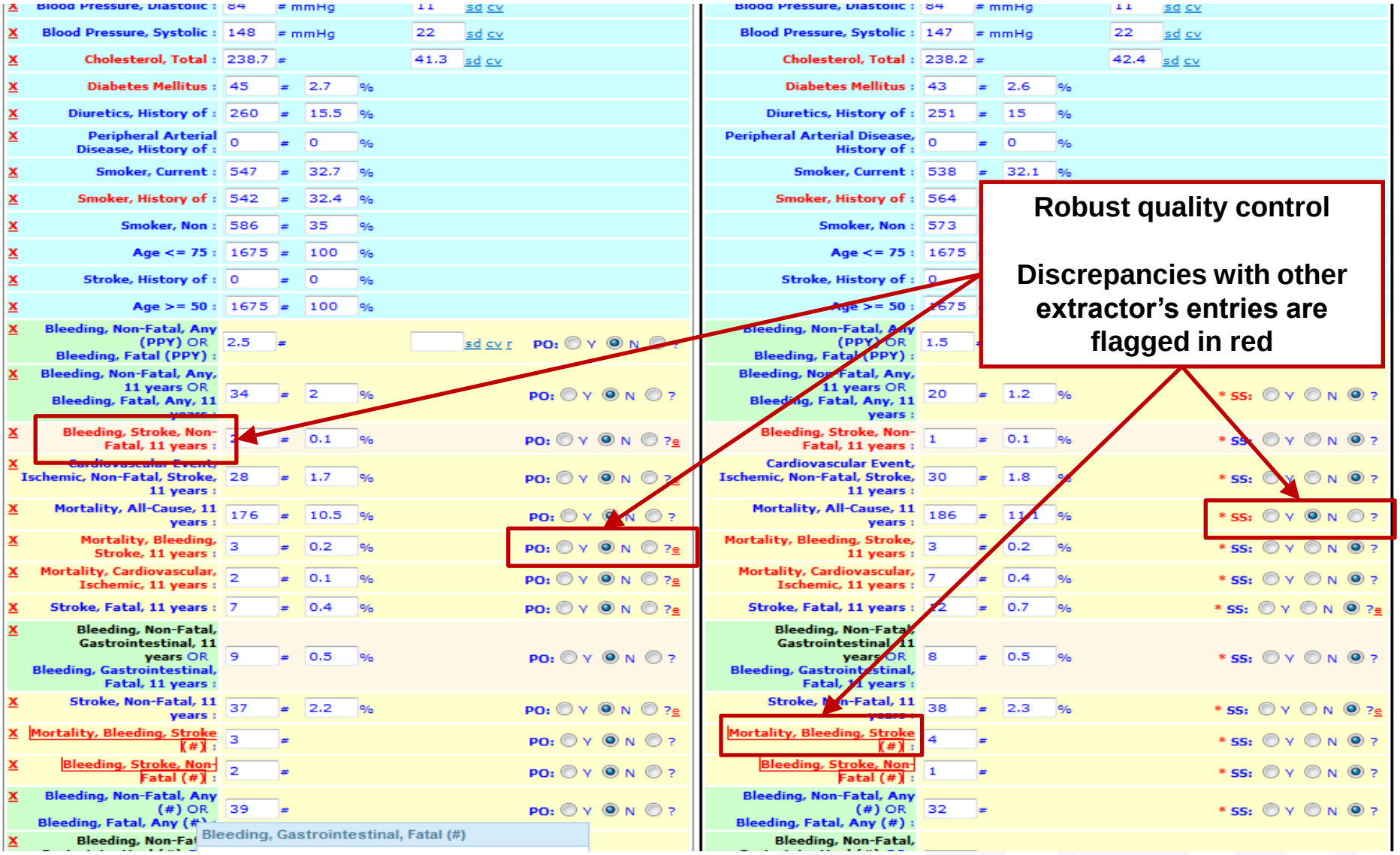
Data Extraction Template



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Data Extraction Adjudication

GROUP: Placebo *OUTCOME: Mortality, Cardiovascular, Ischemic, 11 years* **Is Primary Outcome**	+ note (1)	E. Kim	*N	<--Use Value
		M. Fam	Y	<--Use Value
		Final	*N	
GROUP: Placebo *OUTCOME: Cardiovascular Event, Ischemic, Non-Fatal, Stroke, 11 years* **Is Primary Outcome**	+ note (1)	E. Kim	*N	<--Use Value
		M. Fam	Y	<--Use Value
		Final	*N	
GROUP: Placebo *OUTCOME: Stroke, Fatal, 11 years* **Is Primary Outcome**	+ note (1)	E. Kim	*N	<--Use Value
		M. Fam	Y	<--Use Value
		Final	*N	
GROUP: Placebo *OUTCOME: Stroke, Fatal, 11 years* **SS**	+ note (1)	E. Kim	N	<--Use Value
		M. Fam	*?	<--Use Value
		Final	*?	
GROUP: Placebo *OUTCOME: Stroke, Non-Fatal, 11 years* **SS**	+ note (1)	E. Kim	N	<--Use Value
		M. Fam	*?	<--Use Value
		Final	*?	
GROUP: Placebo *OUTCOME: Stroke, Non-Fatal, 11 years* **Is Primary Outcome**	+ note (1)	E. Kim	*N	<--Use Value
		M. Fam	Y	<--Use Value
		Final	*N	
GROUP: Placebo *OUTCOME: Bleeding, Non-Fatal, Any, 11 years* *OUTCOME: Bleeding, Fatal, Any, 11 years* **AM_CustomDefinition**	+ note (1)	E. Kim	*The risk of an initial event of major hemorrhage was 71% higher in the aspirin group as compared to placebo. Hazard ratio = (# with outcome)/(person time at risk).	<--Use Value
		[illegible]n	The rate of a major hemorrhage requiring admission to hospital was 71% higher in the Aspirin group as compared to the Placebo group.	<--Use Value
			*The risk of an initial event of major hemorrhage was 71% higher in the aspirin group as compared to placebo. Hazard ratio = (# with outcome)/(person time at risk).	
GROUP: Placebo	+ note	[illegible]	[illegible]	[illegible]

Adjudication between discrepant extractions is included in the final template

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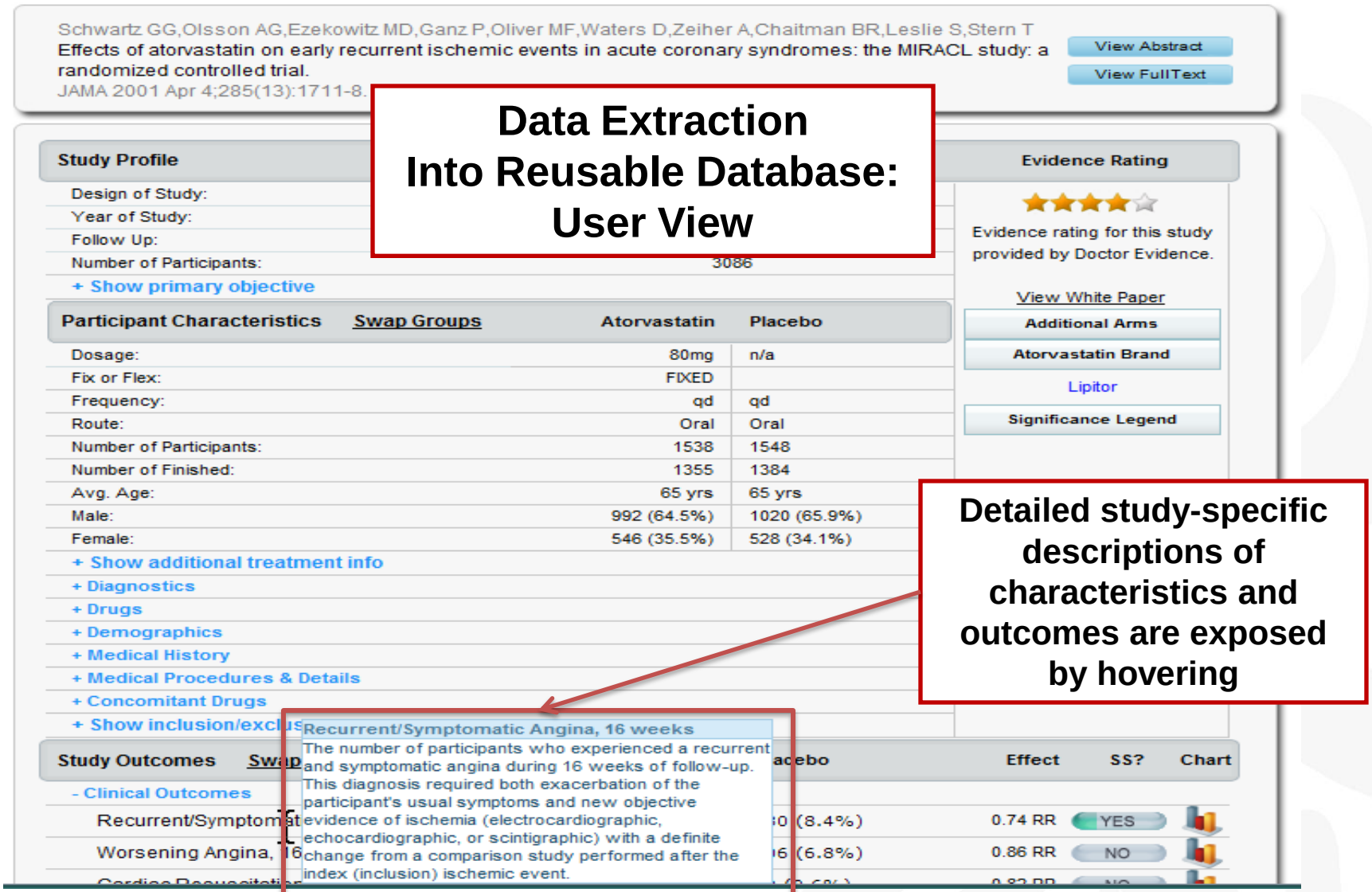
Digitized Study Summary



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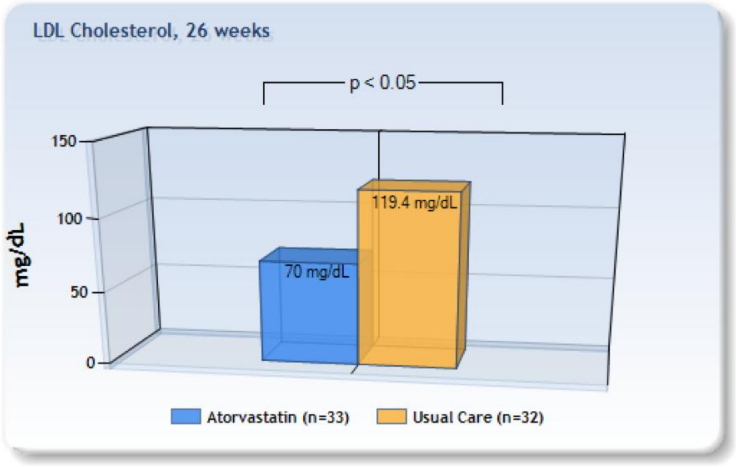
Digitized Study Summary

Study Outcomes	Swap Groups	Atorvastatin	Usual Care	Effect	SS?	Chart
- Clinical Outcomes						
Recurrent Angina, 26 weeks		8 (24.2%)	8 (25%)		NA	
Target Vessel-Related Myocardial Infarction, 26 weeks		0 (0%)	0 (0%)		NA	
- Diagnostics (Surrogates)						
✔ % Change in Plaque Volume, 26 weeks		-13.1 %	8.7 %		YES	
Apolipoprotein A1, 26 weeks		126.4 mg/dL	125.1 mg/dL		NO	
Apolipoprotein B, 26 weeks		66.1 mg/dL	92.6 mg/dL		YES	
Apolipoprotein E, 26 weeks		3.31 mg/dL	4.34 mg/dL		YES	
C-Reactive Protein, 26 weeks		0.09 mg/dL	0.14 mg/dL		NA	
HDL Cholesterol, 26 weeks		46.6 mg/dL	47.4 mg/dL		NO	
LDL Cholesterol, 26 weeks		70 mg/dL	119.4 mg/dL		YES	
Total Cholesterol, 26 weeks					YES	
Lipopr					NO	
Plaque					NO	
Chang					YES	
Triglyc					NO	
- Mortality						
All-Cause Mortality, 26 weeks					NA	
Cardiac Mortality, 26 weeks					NA	
Non-Cardiac Mortality, 26 weeks					NA	
- Medical Procedures						
Coronary Revascularization, 26 weeks					NO	

Graphic display of study outcomes and statistical significance



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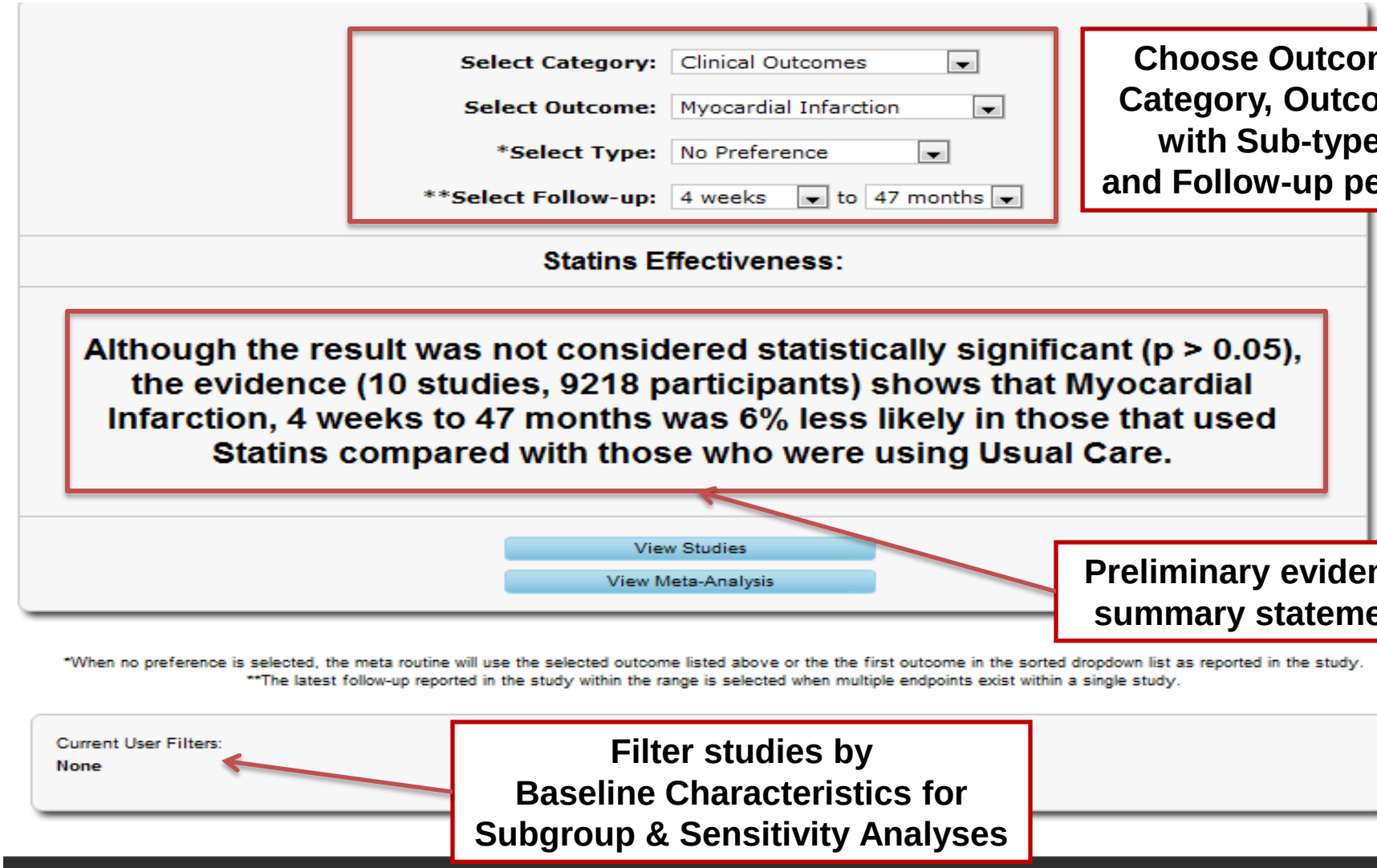
Meta-Analysis



Choose Outcome Category, Outcome with Sub-type, and Follow-up period

Preliminary evidence summary statement

Filter studies by Baseline Characteristics for Subgroup & Sensitivity Analyses

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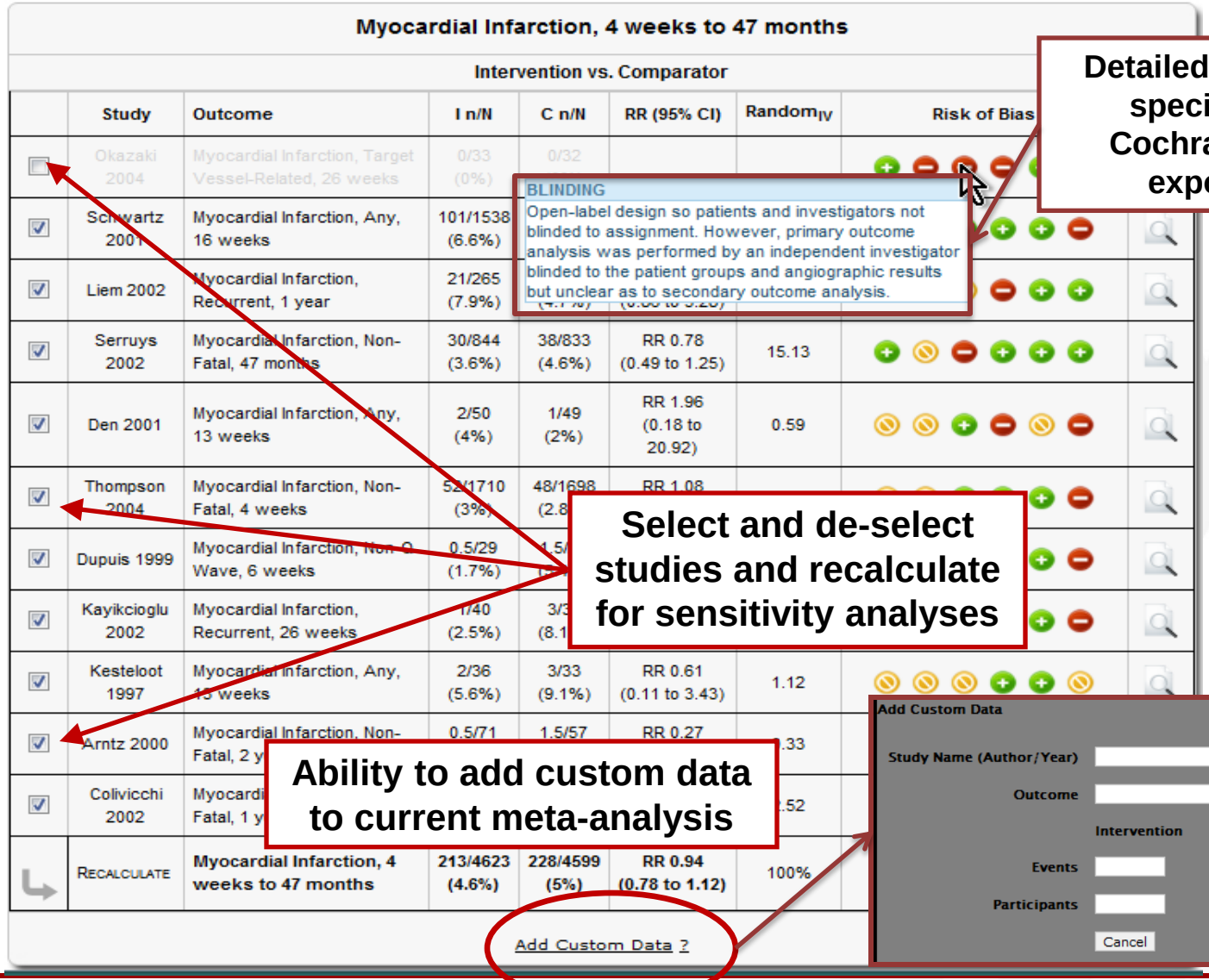
Meta-Analysis Results



Detailed study- and outcome-specific descriptions of Cochrane Risk of Bias are exposed by hovering

Select and de-select studies and recalculate for sensitivity analyses

Ability to add custom data to current meta-analysis

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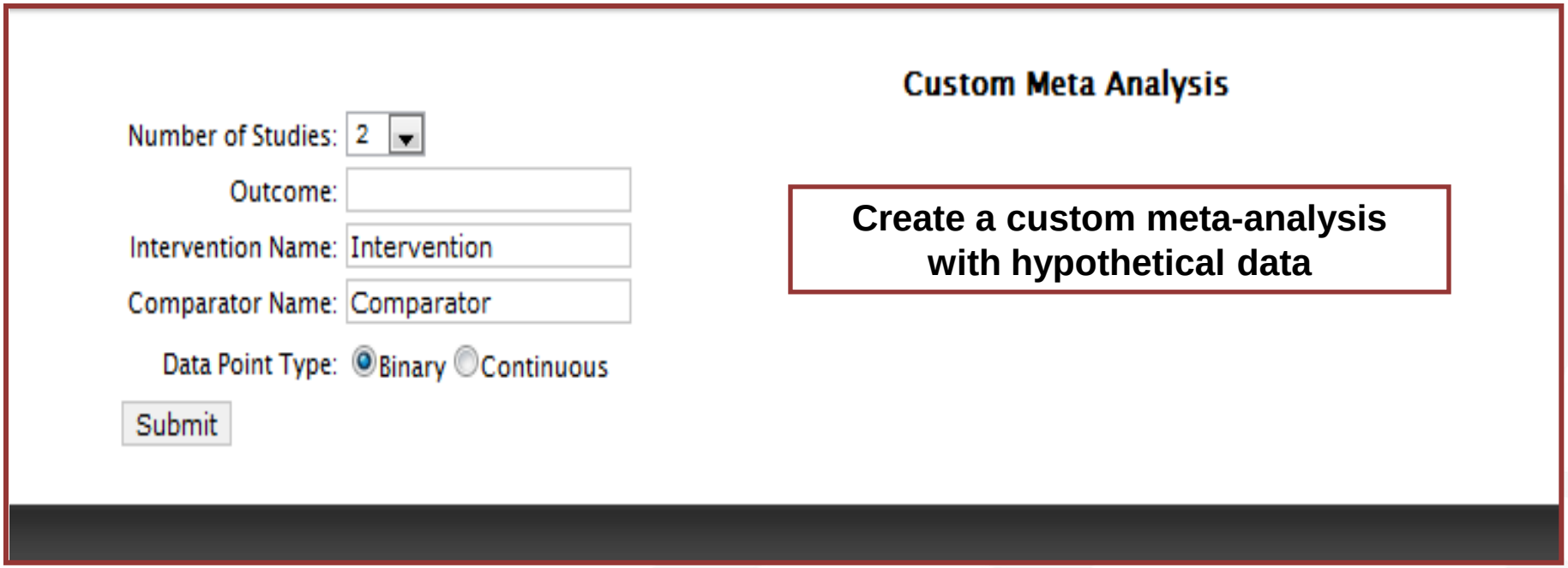
Custom Meta Analysis



Create a custom meta-analysis with hypothetical data

Recreate published meta-analyses with additional data or sensitivity analyses

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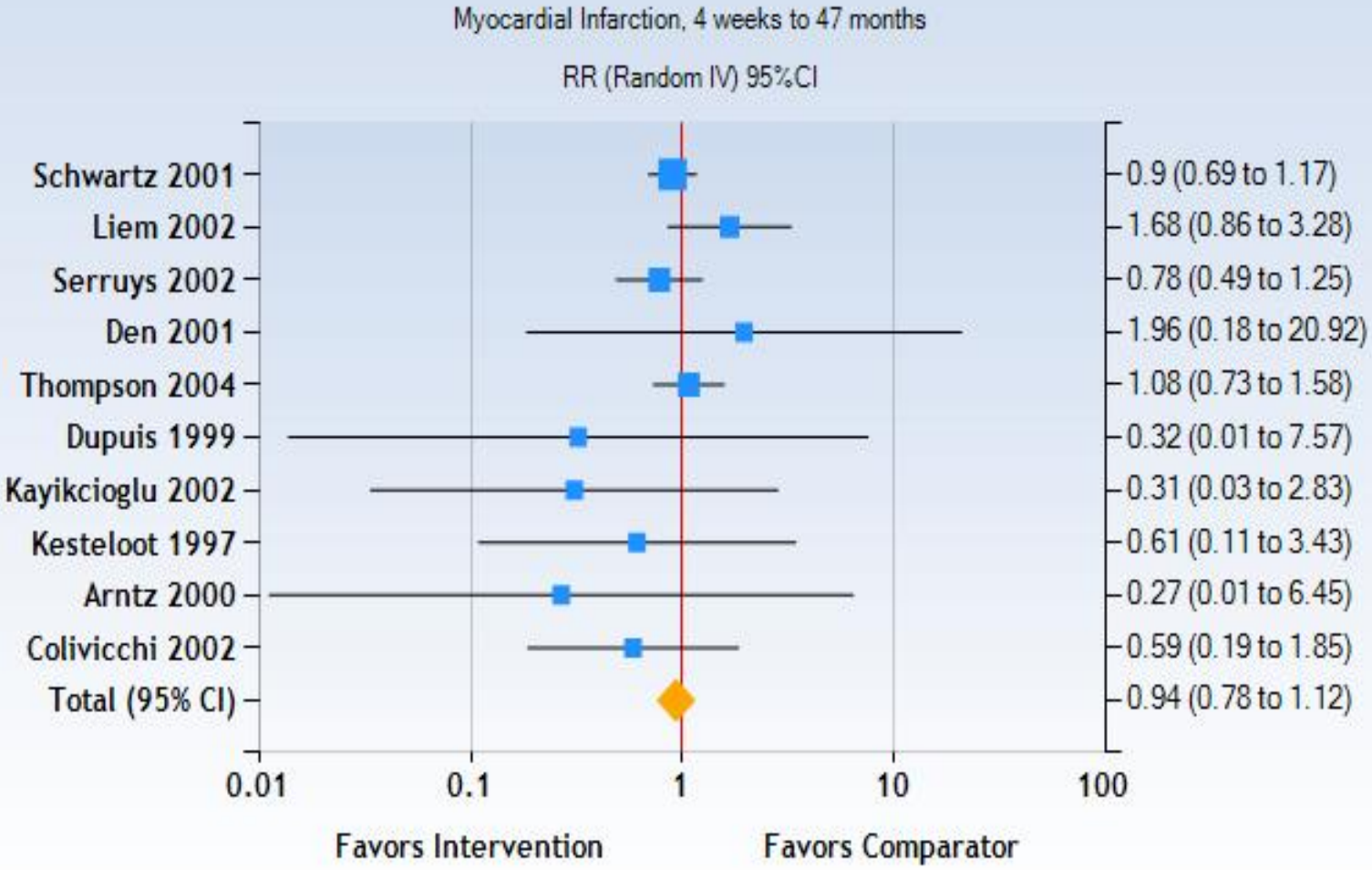
Forest Plot



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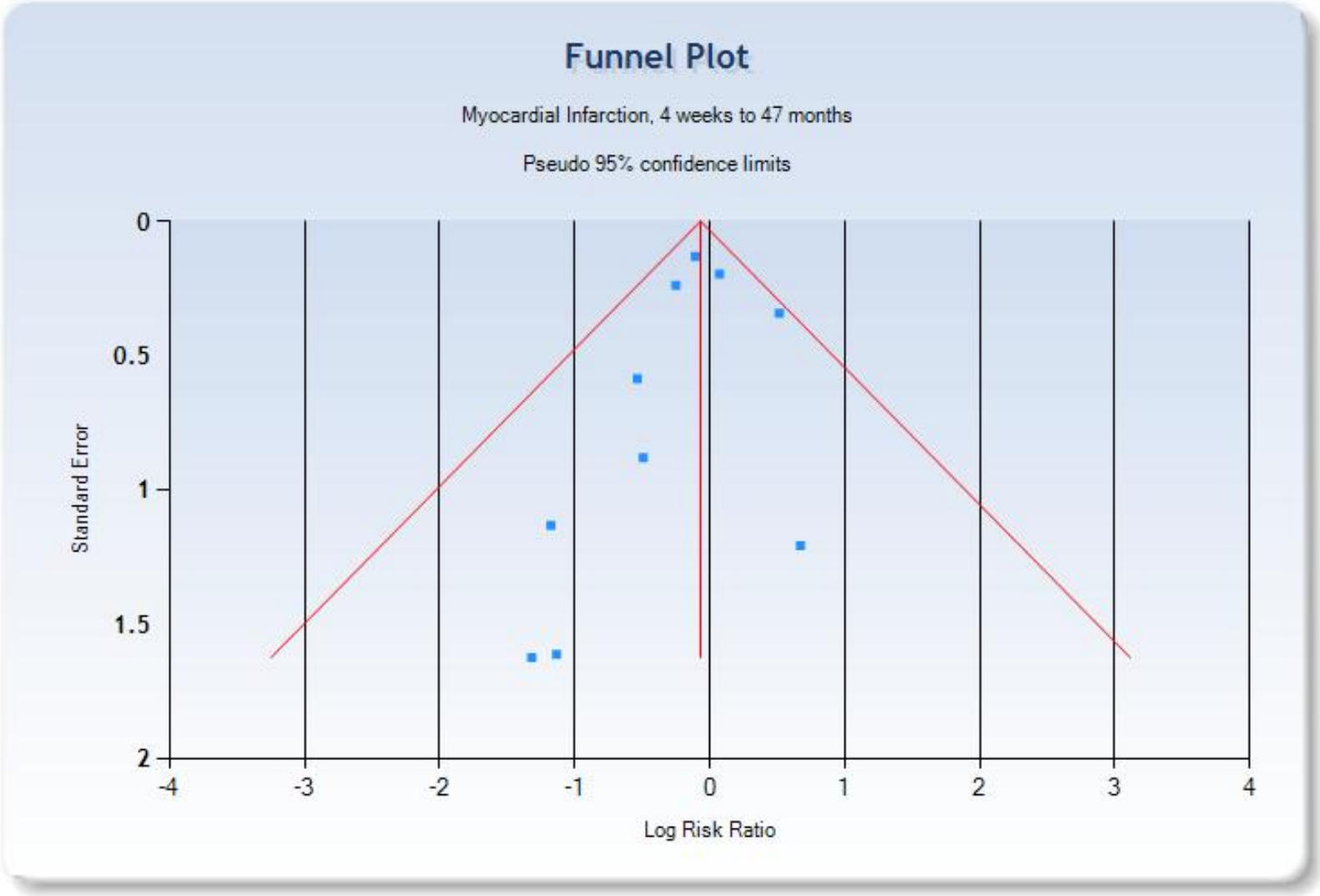
Funnel Plot



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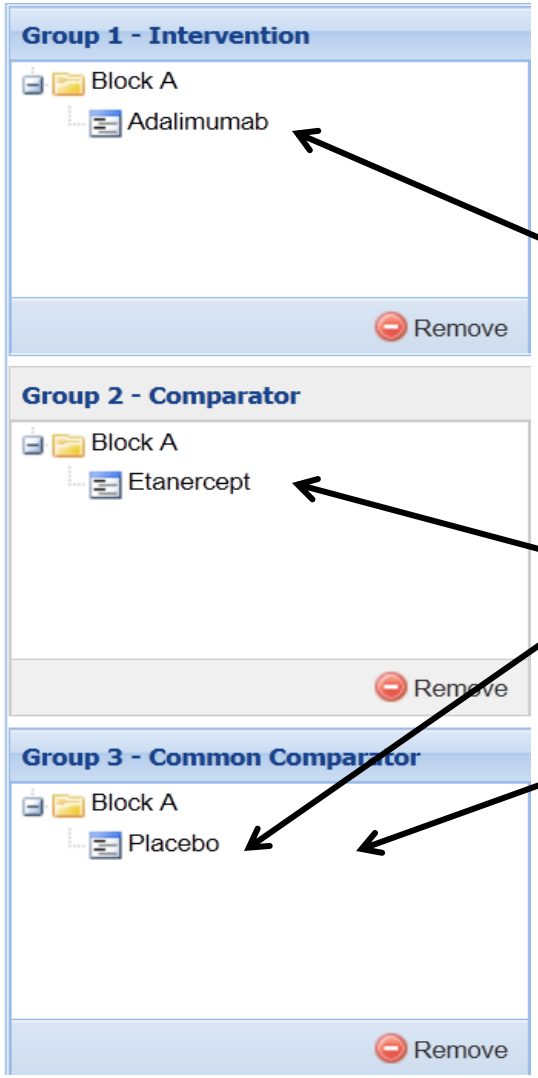
Indirect Meta Analysis



A vs. C

B vs. C

Indirectly compare A vs. B
(Adalimumab vs. Etanercept)

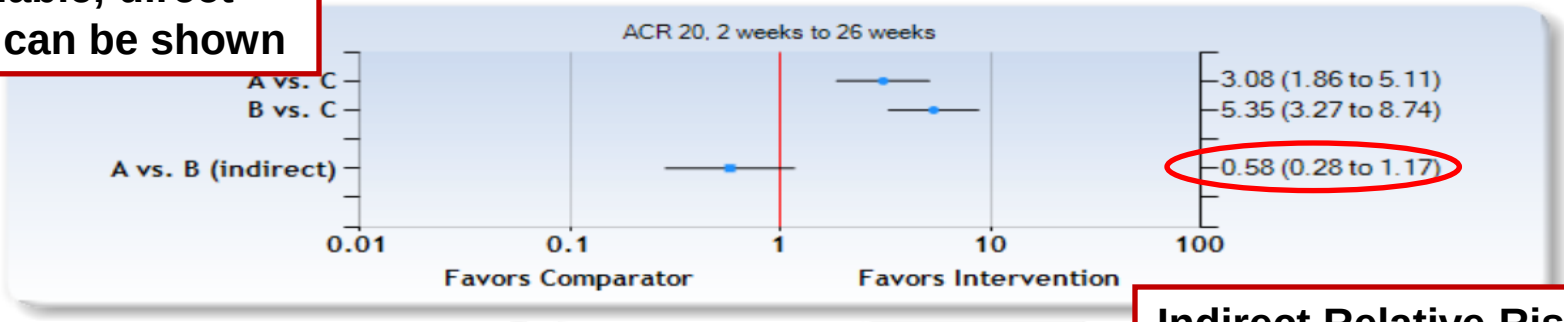
Indirect Meta Analysis: Common Comparison

Intervention - A: Adalimumab
Comparator - B: Etanercept
Common Comparator - C: Placebo

Select Category: Responders
Select Outcome: ACR 20
****Select Follow-up:** 2 weeks to 26 weeks

ACR 20, 2 weeks to 26 weeks				
Comparison	**Number of Trials**	**Risk Ratio (95% CI)**	**I^2%**	
A vs. C	5	3.0811 (1.8566 - 5.1133)	79%	view
B vs. C	2	5.3461 (3.2701 - 8.7399)	0%	view
A vs. B (direct)	0	0 (0 - 0)	N/A	view
A vs. B (indirect)	5/2	0.5763 (0.2845 - 1.1674)		

If available, direct analysis can be shown



Indirect Relative Risk

Meta Analysis Statistical Settings

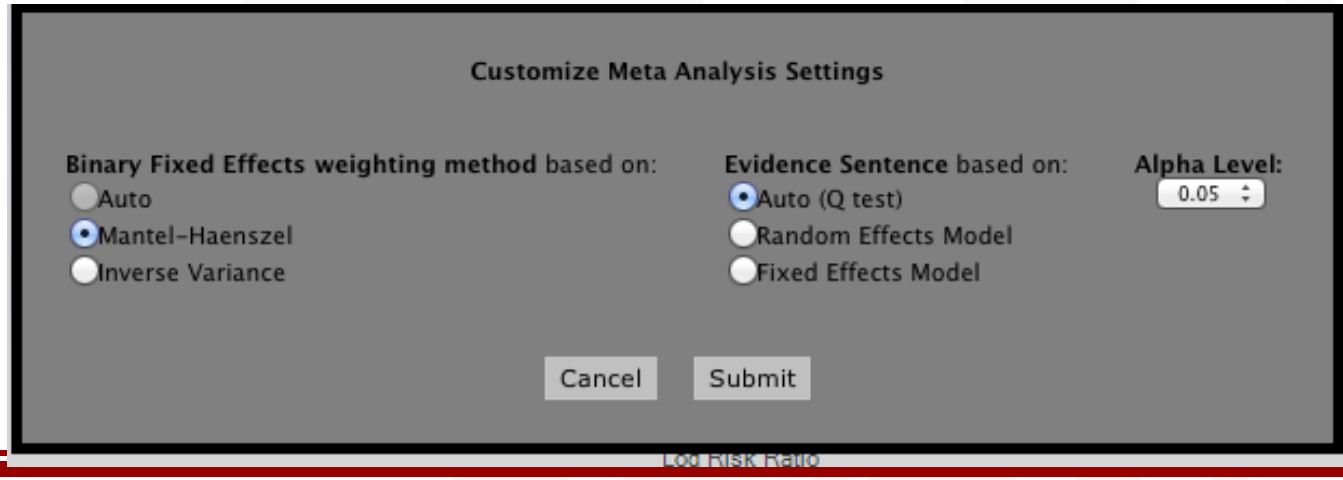
General				
Number of studies: 10				
Number of participants: 9218				
Results				
Model	Risk Ratio	99% CI	z	p-value
Fixed Effects$_{MH}$	0.9346	0.7365 to 1.1859	0.733	0.4636
Fixed Effects$_{IV}$	0.9353	0.7357 to 1.1892	0.7183	0.4726
✓ Random Effects$_{IV}$	0.9353	0.7357 to 1.1892	0.7183	0.4726
Quantifying Heterogeneity				
tau^2: 0	H: 0.9018	I^2: 0%		
Test of Heterogeneity				
Q_{IV}: 7.3189	DF: 9	p: 0.604		

Settings	
Alpha:	0.01
Design:	Any Design
Blinding:	Any Blinding
Control:	None or Placebo or Usual Care
Analysis Type:	ITT and PP
Follow Up:	Any Followup
Participants:	Any # of Participants
Sentence:	Random Model
Binary Fixed Weights:	Inverse Variance

Change Settings

*Meta-Analysis using Inverse Variance method (view)

Capable of changing Meta Analysis settings to various weighting methods and modeling



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Generate Evidence Tables

Evidence Table Wizard

Step 5: Preview / Generate Table | Number of Studies: 13 [Reset All] | < Back | Generate Excel

Preview Evidence Table

Study	Design	N	Length	Interventions	Dose	n	Mean Age	% Female	Cholesterol, Total	Cholesterol, LDL	Cholesterol, HDL	Diabetes Mellitus	ACE-Inhibitor, Concomitant	Beta Blocker, Concomitant	Myocardial Infarction, History of	Smoker, Current	Hypertension	Aspirin, Concomitant
Arntz 2000	RCT	135	2 yrs	Pravastatin	20-40mg	70	55yrs	19%	237mg/dL	176mg/dL	31mg/dL	0%	18%	37.7%	64%		31%	
				Usual Care	_	65	59yrs	21%	223mg/dL	172mg/dL	32mg/dL	0%	25%	52%	70%		32%	

Primary Objective: The combined clinical end points were total mortality, cardiovascular death, nonfatal myocardial infarction, need for coronary intervention, stroke, and new onset of peripheral vascular disease. Nonfatal myocardial infarction, coronary balloon angioplasty or bypass grafting, stroke, new onset of occlusive peripheral vascular disease, cardiovascular death, and all-cause mortality were prospectively defined as secondary end points.

Primary Outcome(s): Mortality, All-Cause OR Stroke, Any OR Myocardial Infarction, Non-Fatal OR Mor

Inclusion/Exclusion: Patients with total cholesterol of > 200 to < 400 mg/dl and low-density lipoprotei
hyperlipidemia) with an acute myocardial infarction (defined by new Q waves and increase of enzymes
transluminal coronary balloon angioplasty due to severe or unstable angina pectoris (defined by clinics
were included in this study. Patients with an acute infarction were included only if their lipids could be determined within 8 hours after onset of symptoms; those in the balloon angioplasty group with a history of infarction were included only when the infarction was >= 3 months earlier. Patients > 75 years old, diabetics (fasting blood glucose > 125 mg/dl), patients with postcoronary artery bypass graft, known malignant disease, serious kidney or liver dysfunction (creatimine > 1.5 mg/dl, alanine aminotransferase and aspartate aminotransferase > 2 times normal value), or women of child-bearing age not using a reliable form of contraception were excluded.

Additional Treatment Info: Treatment began an average of 6 (+/- 5) days after qualifying event. Patients in this group with a baseline LDL cholesterol level of <160 mg/dl initially received pravastatin 20 mg/dl; those with an LDL cholesterol of >=160 mg/dl received 40 mg/day. To achieve LDL cholesterol levels of <=130 mg/dl, the pravastatin dosage was increased to 40 mg/day, and nicotinic acid (1.5 to 6 g/day) and/or cholestyramine (4 to 32 g/day) were added if necessary. Antilipidemic therapy was determined by the family physician.

Risk Of Bias:
Sequence Generation: UNCLEAR - No information about the sequence generation process
Allocation Concealment: HIGH - Open-label design.
Blinding: HIGH - Open-label – patients not blinded- potential selection bias (9/65 randomized to 'usual care' dropped out after knowledge of tx.
Incomplete Outcome Data: LOW - Described for primary outcome: those without evaluable angiographies had similar reasons for missing outcomes; Drop outs would not have changed interpretation of outcomes.
Selective Outcome Reporting: LOW - The study protocol was not available, but adequate detail given to specification of primary and secondary outcomes.
Other Sources of Bias: HIGH - Not a placebo controlled trial: protocolized statin tx vs usual care; therefore control group may have been treated.

Characteristic Definitions: Cholesterol, Total: The mean total cholesterol level for participants at baseline. **Cholesterol, LDL:** The mean LDL cholesterol level for participants at baseline. **Cholesterol, HDL:** The mean HDL cholesterol level for participants at baseline. **Diabetes Mellitus:** The number of participants who are diabetic. **ACE-Inhibitor, Concomitant:** The number of participants taking ACE (Angiotensin-Converting Enzyme) inhibitors during the study period. **Beta Blocker, Concomitant:** The number of participants taking a beta blocker concomitantly.

Customizable, Automated Evidence Table Generation