



Accelerating and Reducing the Cost of Literature Reviews and Regulatory Dossiers for Rare Diseases with AI

Meelis Lootus, Ph.D
CEO & Founder
Tehistark

meelis@tehistark.com

Problem: Constraints Compound for Treatment Innovation to Rare Diseases

Limited Data



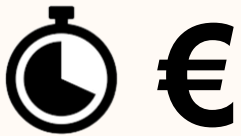
6000 diseases
Variable manifestations

Regulatory Complexity

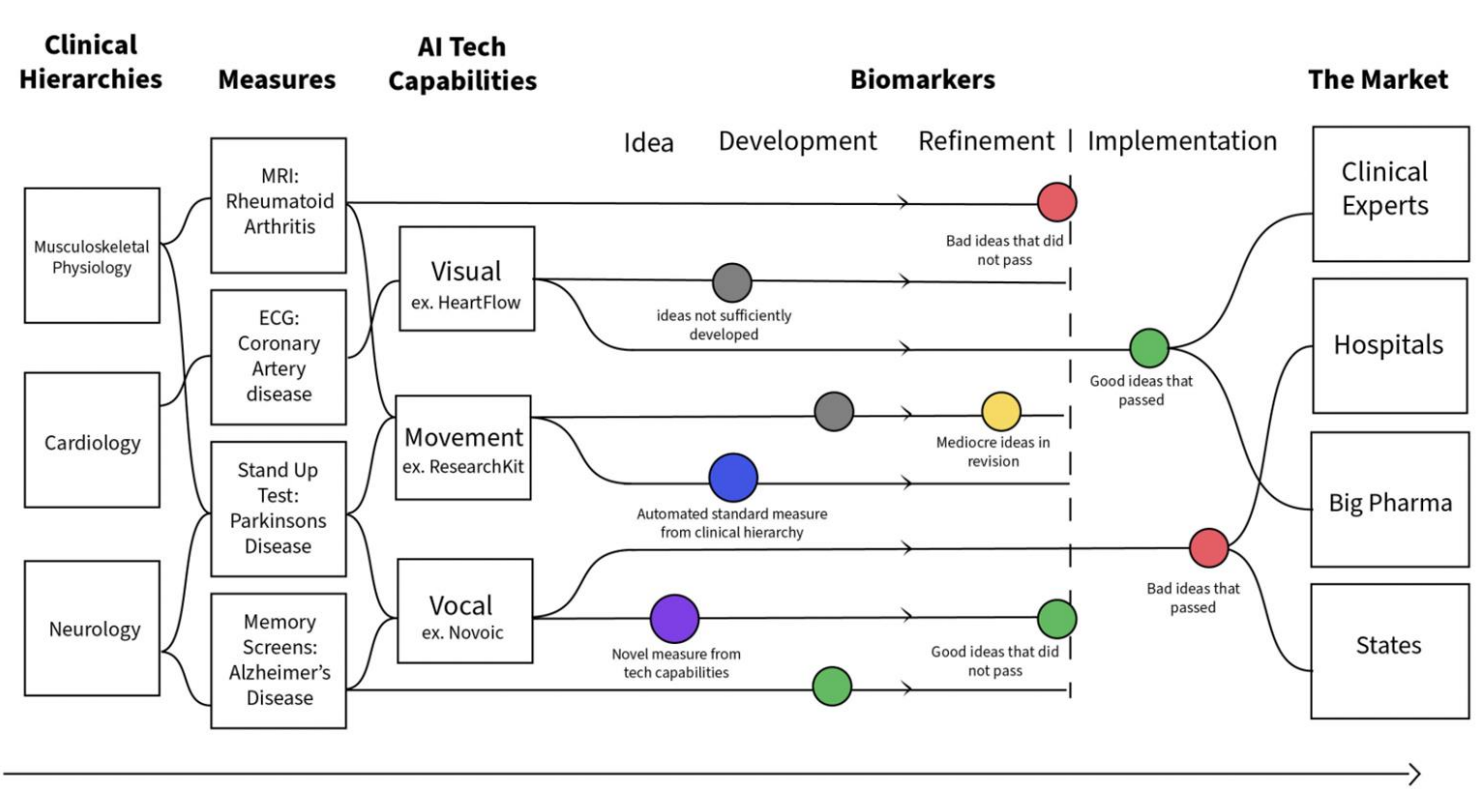


EMA, national, and global frameworks.
Evolving guidelines
Inconsistencies across jurisdictions.

Resource Constraints



Example: The Uncertain Landscape of Digital Measurement Devices to the Market



Example: Developing Solutions for Myasthenia Gravis (MG)

Completed 1 **1. Write Protocol**

Help Build an A.I. Model to Predict Myasthenia Gravis Symptom Patterns and Flares

ClinicalTrials.gov ID 1 NCT04590716

Sponsor 1 doc.ai inc

Information provided by 1 doc.ai inc (Responsible Party)

Last Update Posted 1 2021-07-29

2. Collect Data

> [Front Neurol.](#) 2023 Aug 1;14:1144183. doi: 10.3389/fneur.2023.1144183. eCollection 2023.

A decentralized, prospective, observational study to collect real-world data from patients with myasthenia gravis using smartphones

[Sandra Steyaert](#)^{1 2}, [Meelis Lootus](#)¹, [Chethan Sarabu](#)¹, [Zeena Framroze](#)¹, [Harriet Dickinson](#)³, [Emily Lewis](#)⁴, [Jean-Christophe Steels](#)⁴, [Francesca Rinaldo](#)¹

Affiliations + expand
PMID: 37588667 PMCID: [PMC10427188](#) DOI: [10.3389/fneur.2023.1144183](#)

Abstract

Introduction: We conducted a 3-month, prospective study in a population of patients with Myasthenia Gravis (MG), utilizing a fully decentralized approach for recruitment and monitoring (ClinicalTrials.gov Identifier: [NCT04590716](#)). The study objectives were to assess the feasibility of collecting real-world data through a smartphone-based research platform, in order to characterize symptom involvement during MG exacerbations.

3. Use Data for Decisions, Planning

> [Digit Biomark.](#) 2023 Jul 28;7(1):63-73. doi: 10.1159/000531224. eCollection 2023 Jan-Dec.

Development and Assessment of an Artificial Intelligence-Based Tool for Ptosis Measurement in Adult Myasthenia Gravis Patients Using Selfie Video Clips Recorded on Smartphones

[Meelis Lootus](#)¹, [Lulu Beatson](#)¹, [Lucas Atwood](#)¹, [Theo Bourdais](#)¹, [Sandra Steyaert](#)², [Chethan Sarabu](#)¹, [Zeena Framroze](#)¹, [Harriet Dickinson](#)³, [Jean-Christophe Steels](#)⁴, [Emily Lewis](#)⁴, [Nirav R Shah](#)⁵, [Francesca Rinaldo](#)¹

Affiliations + expand
PMID: 37545566 PMCID: [PMC10399113](#) DOI: [10.1159/000531224](#)

Abstract

Introduction: Myasthenia gravis (MG) is a rare autoimmune disease characterized by muscle weakness and fatigue. Ptosis (eyelid drooping) occurs due to fatigue of the muscles for eyelid elevation and is one symptom widely used by patients and healthcare providers to track progression of the disease. Margin reflex distance 1 (MRD1) is an accepted clinical measure of ptosis and is typically assessed using a hand-held ruler. In this work, we develop an AI model that enables automated measurement of MRD1 in self-recorded video clips collected using patient smartphones.



Use and impact

Solution: AutoDossier to make High Quality Dossiers Fast

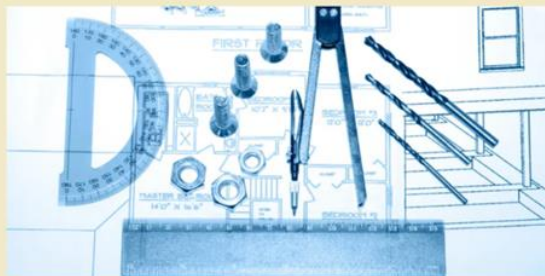
WHAT IS AUTODOSSIER AND HOW DOES IT WORK?

Step 1: Upload your data



Upload to secure platform. No organisation required.

Step 2: Go for coffee



AI completes a first draft (or several different versions) fully autonomously, for you to iterate on.

Step 3: Review and iterate



Return to a completed first draft - much faster than starting from scratch - with source data shown. Iterate faster and better with AI assistance.

Solution: AutoDossier to make High Quality Dossiers Fast

WHAT DOCUMENTS CAN YOU CREATE ON AUTODOSSIER?

Literature Reviews:
Rapid, Targeted,
Systematic

Search
Screen
Extract
Synthesize

IND & CTA

CMC
Toxicology
Pharmacology
Pharmacokinetics

HTA

Clinical
Economic

AutoDossier: How do we use AI

MVP pilot-ready!
(Secure Usable Cloud Platform)

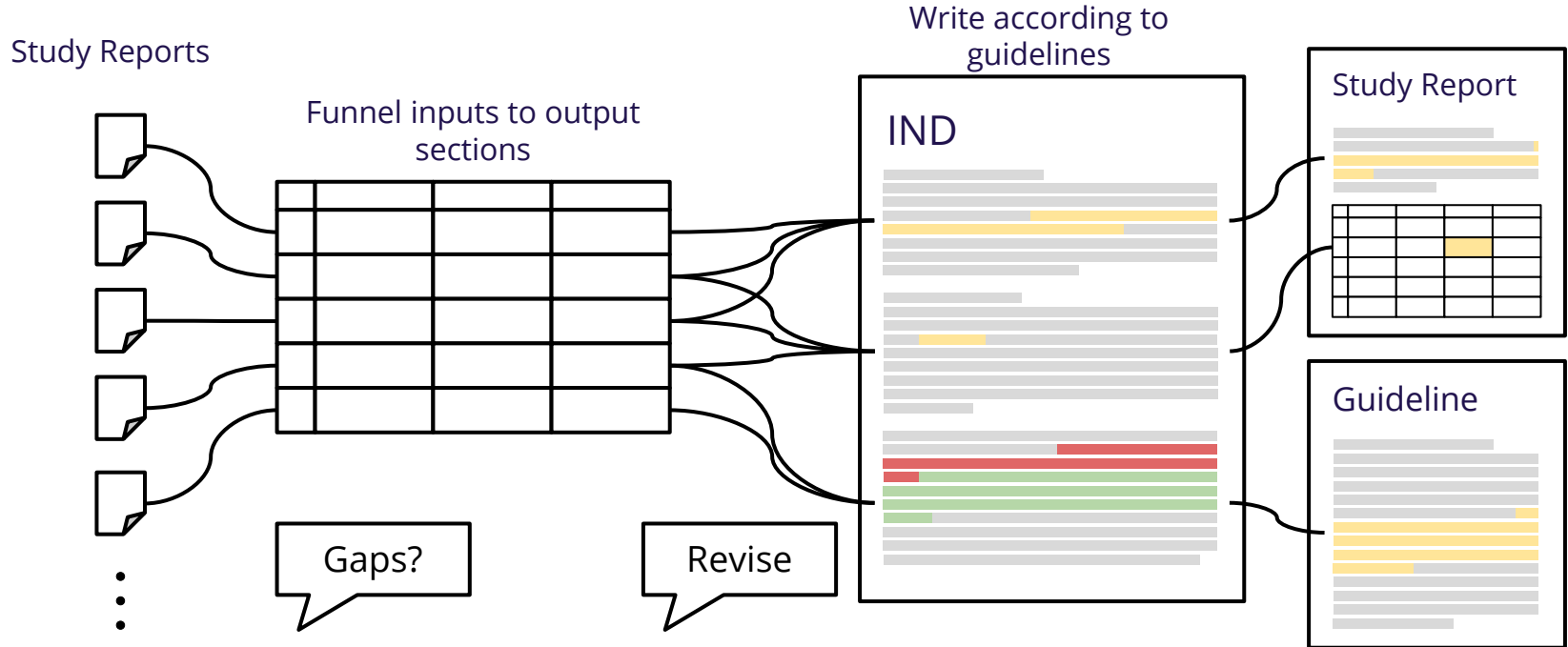
Draft the **IND in minutes**, by optimally combining AI and human input.

1. Upload inputs

2. Route, find gaps

3. Auto-draft

4. Verify & Revise



Demo 1: Writing an IND

1 INPUT 2 ROUTE 3 WRITE 4 OUTPUT

Input Documents

File

Drop File Here
- or -
Click to Upload

- OR -

Sharepoint Link

0 / 0 Files Ready

Filename	Status
----------	--------

Dossier

Indication

Route of Administration

Dossier Type
Clinical Trial Approval (IND, CTA)

Select Regions and Bodies (Select All That Apply)

US - FDA EU - EMA UK - MHRA JP - PMDA CAN - HC UAE - ADAFSA CAN - CAANS/ACAE More...

Write Dossier

Project

new-proj

proj-001
Molecule XYZ (IND)
Oncology
Toxicology complete.

proj-003-neuro-18-srs
Molecule Neurotox (IND)
Neurology
Toxicology complete. Clinical trial 1 ongoing

Demo 2: Gap Analysis

1 INPUT 2 ROUTE 3 WRITE 4 OUTPUT

Input Documents

- SR1_AcuteToxMice
- SR2_ChronicToxRats**
- SR3_PK_Rabbits
- SR4_PD_mice
- SR5_Carc_Rodent
- SR10_BA_dogs
- SR11_ME_pigs
- SR12_Cardio_primate

0	0	1.0
10	0	0.98
20	5	0.85
30	10	0.70

Chronic Toxicity Study in Rats

Introduction

This comprehensive report outlines the results of a 6-month chronic toxicity study conducted on rats to evaluate the long-term effects of Olanzapine. The study primarily focused on assessing potential liver and kidney stress associated with higher doses of the drug. The aim was to establish a clear understanding of the chronic toxicity profile of Olanzapine, providing essential data for its safety evaluation over prolonged exposure periods.

Protocol

Measurement Methodology
Dosages of 0, 10, 20, and 30 mg/kg/day were administered orally to four groups of rats, with each group receiving one of the dosages respectively.

Experimental Setup
80 rats (40 males, 40 females) were randomly assigned to the four experimental groups. The administration of the drug was conducted daily for six months, with continuous monitoring of general health and behavioral changes.

Results

In the 20 and 30 mg/kg/day dosage groups, notable signs including weight loss and decreased activity were observed, indicating potential adverse effects at higher dosages. Contrarily, the groups receiving 0 and 10 mg/kg/day displayed no significant adverse effects.

Table 1: Summary of Health Outcomes by Dosage
Percentage of weight loss and normalized activity levels for each dosing group over the 6-month study period.

Discussion

The findings from this chronic toxicity study suggest a dose-dependent toxicity of Olanzapine in rats, particularly at dosages of 20 and 30 mg/kg/day. The observed adverse effects primarily include weight loss and decreased activity levels. These symptoms are indicative of potential liver and kidney stress, necessitating further investigation and possibly adjustment of dosage recommendations for longer-term administration in clinical settings.

Conclusion

This study highlights the importance of dose management in the chronic administration of Olanzapine, emphasizing safety concerns that must be addressed before long-term human exposure. Our data supports the need for additional research to optimize the dosage and reduce toxicity, ensuring the therapeutic efficacy of Olanzapine while minimizing potential risks.

Options

- ▼ M2.6.6 Toxicology Written Summary
- ▼ M2.6.6.2 Single-Dose Toxicity
- Acute Toxicity and Tolerability in Mice**

In the study "Acute Toxicity and Tolerability in Mice," healthy adult mice of mixed sexes, approximately 8 weeks old, were used to evaluate the acute toxicity and tolerability of Olanzapine. A total of 12 mice per group were administered single doses of Olanzapine ranging from 5 mg/kg to 50 mg/kg via intraperitoneal injection. The study duration was 72 hours post-administration during which mice were observed for signs of toxicity such as lethargy, reduced mobility, and other symptoms. Data on mortality, morbidity, and clinical signs of toxicity were systematically recorded at 24, 48, and 72 hours. Post-mortem examinations were conducted in cases of mortality to ascertain the cause of death.

In the "Acute Toxicity and Tolerability in Mice" study, no deaths occurred at doses of 5 to 25 mg/kg of Olanzapine with no signs of toxicity observed; however, mortality increased significantly with higher doses, reaching 41.67% at 50 mg/kg. Notable adverse events included lethargy, reduced mobility, reduced food intake, disorientation, and seizures at higher doses, suggesting a dose-dependent increase in severity and incidence of toxicity signs. Clinical observations were systematically recorded, and post-mortem examinations were conducted to ascertain causes of death, confirming the relationship between dose and toxicity. The study concluded that Olanzapine appears safe at doses up to 20 mg/kg based on the absence of mortality and adverse effects at these levels. This threshold of safety suggests that higher doses pose significant risks, necessitating further investigation into the drug's pharmacodynamics and safe application in clinical settings.

- ▼ M2.6.6.3 Repeat-Dose Toxicity
- Chronic Toxicity Study in Rats**

In a 6-month chronic toxicity study, 80 rats (40 males and 40 females) were administered Olanzapine orally at dosages of 0, 10, 20, and 30 mg/kg/day, with each group assigned to one of these dosages. The study aimed to evaluate the potential chronic toxicity of Olanzapine, particularly focusing on liver and kidney stress. The dosing and observation were conducted daily throughout the study duration, assessing general health and behavioral changes. Data collected included weight loss percentages and normalized activity levels, which indicated dose-dependent toxicity at higher dosages. The results revealed significant adverse effects such as weight loss and reduced activity primarily in the 20 and 30 mg/kg/day groups, suggesting the need for further investigation into dosage adjustments for long-term use.

In the "Chronic Toxicity Study in Rats," no deaths were reported across any dosage groups during the six-month study period, indicating that Olanzapine was not lethal at the administered dosages. Measurements taken included percentage weight loss and activity levels, where increased dosage led to significant weight loss and reduced activity in the 20 and 30 mg/kg/day groups. Specifically, the 20 mg/kg group experienced a 5% weight loss and a decrease in activity to 0.85, while the 30 mg/kg group saw a 10% weight loss and activity reduced to 0.70. Adverse effects noted were dose-dependent, with significant findings including potential liver and kidney stress suggested by symptoms like weight loss and decreased activity at higher doses. The study concluded that careful dose management is crucial in long-term administration of Olanzapine to mitigate potential toxic effects and optimize therapeutic efficacy.

Generate Export



Demo 3: Updating an IND

1 INPUT 2 ROUTE 3 WRITE 4 OUTPUT

Report-Level Routing Study-Level Routing Element-Level Routing Gap Analysis

Options

Indication
Oncology

Mode
 Requirement analysis Gap analysis No labels

View
 Show full dossier Show only required items Show only missing items
 Show only writing-ready items

▼ M2 Common Technical Document Summaries 4/13 missing

▼ M2.6 Nonclinical Written And Tabulated Summaries 4/13 missing

- ▼ M2.6.2 Pharmacology Written Summary 3/7 missing
 - ▶ M2.6.2.2 Primary Pharmacodynamics 3 complete
 - ▶ M2.6.2.5 Pharmacodynamic Drug Interactions 3 missing
- ▼ M2.6.3 Pharmacology Tabulated Summary 1/1 missing
 - ▶ M2.6.3.1 Pharmacology Overview 3 complete
 - ▶ M2.6.3.2 Primary Pharmacodynamics complete
 - ▶ M2.6.3.5 Pharmacodynamic Drug Interactions 1 missing
- ▼ M2.6.4 Pharmacokinetics Written Summary 1/4 missing
 - ▶ M2.6.4.3 Absorption 3 complete
 - ▶ M2.6.4.5 Metabolism (Interspecies Comparison) 1 complete
 - ▶ M2.6.4.6 Secretion 3 missing
 - ▶ M2.6.4.7 Pharmacokinetic Drug Interactions 1 missing
- ▼ M2.6.5 Pharmacokinetics Tabulated Summary 1/5 missing
 - ▶ M2.6.5.1 Pharmacokinetics Overview 3 complete
 - ▶ M2.6.5.3 Absorption After A Single Dose 1 complete
 - ▶ M2.6.5.10 Pharmacokinetics: Metabolism In Vitro complete
 - ▶ M2.6.5.13 Pharmacokinetics: Excretion complete
 - ▶ M2.6.5.15 Pharmacokinetics: Drug-Drug Interactions missing
- ▶ M2.6.6 Toxicology Written Summary 3/2 complete
- ▶ M2.6.7 Toxicology Tabulated Summary 3/3 complete

Input Documents

- SR1_AcuteToxMice
- SR2_ChronicToxRats
- SR3_PK_Rabbits
- SR4_PD_mice
- SR5_Carc_Rodent
- SR10_BA_dogs
- SR11_ME_pigs
- SR12_Cardio_primate

Table 1: Results of Single-Dose Toxicity Assessment

Dose (mg/kg)	Number of Mice	Mortality Rate (%)	Signs of Toxicity	Common Toxicity Signs
5	12	0.00	None	-
10	12	0.00	None	-
15	12	0.00	None	-
20	12	0.00	None	-
25	12	0.00	Mild	Lethargy
30	12	8.33	Mild	Lethargy, Reduced Mobility
35	12	16.67	Moderate	Lethargy, Reduced Mobility, Reduced Food Intake
40	12	25.00	Moderate	Lethargy, Reduced Mobility, Reduced Food Intake, Disorientation
45	12	33.33	Severe	Lethargy, Reduced Mobility, Reduced Food Intake, Disorientation, Agitation

Acute Toxicity and Tolerability in Mice

Protocol

Objective: To evaluate the acute toxicity and tolerability of Olanzapine in mice.

Animals: Healthy adult mice, approximately 8 weeks old, mixed sexes.

Drug Preparation: Olanzapine prepared in appropriate vehicle at concentrations to administer doses of 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 mg/kg.

Dosing: Mice are randomly assigned to groups (n=12 per group). Each group receives a single dose of Olanzapine via intraperitoneal injection.

Observation Period: Mice are observed for 72 hours post-administration for signs of toxicity.

Clinical Observations: Regular monitoring for mortality, behavioral changes, and physical signs of toxicity (e.g., lethargy, reduced mobility).

Data Recording: All observations are recorded systematically for each mouse.

Measurement Methodology

AutoDossier: Benefits

WHAT ARE THE BENEFITS OF AUTODOSSIER?

Higher quality, more transparent work

Ground your applications in the optimal content. Draft with the help of AI. It takes less time to review than to generate from scratch.

Less Expert time spent on Admin Work

Let AI do the heavy lifting on repetitive work, and ask its second opinion on narration, or work out the most fitting narrative with its assistance.

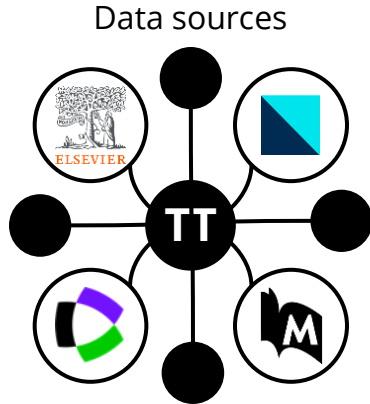
Faster to Market

Thanks to time saved with AI-based document organisation and narrative suggestions, you are able to cut months off project timelines.

Ground the therapeutic program in clinical and market context **better, cheaper, faster**

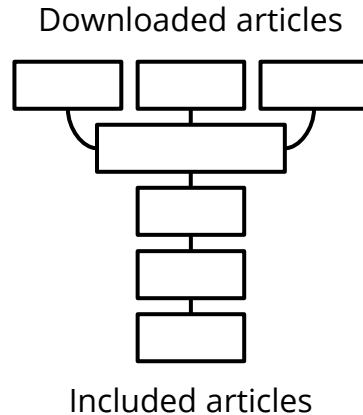
1 Study Setup

- Sculpt your **research question**
- Craft or upload methodology
- **Article Harvester**
 - Directly from databases



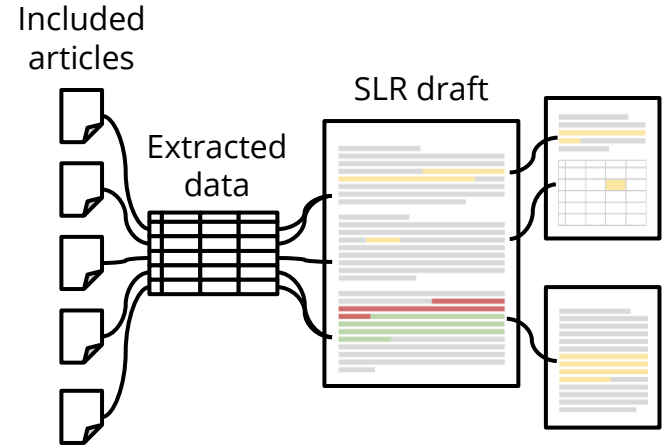
2 PRISMA Machine

- Duplicate removal
- Relevance screening
- Quality screening



3 Extract-Analyse-Write

- Extract relevant data
- Analyse and iterate
- Write the SLR draft



Demo 4: AutoSLR

The screenshot displays the AutoSLR web interface with a progress bar at the top containing four steps: 0 FILE, 1 SETUP-SEARCH, 2 PRISMA-SCREEN, and 3 EXTRACT-ANALYSE-WRITE. Below the progress bar, two sub-steps are visible: 0.1 LOAD PROJECT and 0.2 PROJECT HISTORY. The main content area is titled "Select project" and features a dropdown menu with the selected option "Nielson - Chemotherapy RDI and Cancer Survival (Completed)". Below the dropdown, the project details are listed: "Project name: Nielson - Chemotherapy RDI and Cancer Survival (Completed)", "Directory: /Users/lu/tehistark/mariner/applications/slr_v2/user_data/proj-004", and "UUID: proj-004". The "Run Settings" section includes a "Chat Completion Model" dropdown set to "gpt-3.5-turbo-0125 (context=16000k)" and a checked checkbox for "Full Text Enabled". The "Mode" is set to "Full Auto". The "Enable manual edits" checkbox is unchecked. Under "Data Constraints", the "Max articles to PRISMA" is set to 50, "Max articles to full-text PRISMA" is set to 10, and "Max articles to Extract" is set to 5.

0 FILE 1 SETUP-SEARCH 2 PRISMA-SCREEN 3 EXTRACT-ANALYSE-WRITE

0.1 LOAD PROJECT 0.2 PROJECT HISTORY

Select project

Select Project

Nielson - Chemotherapy RDI and Cancer Survival (Completed)

Project name: Nielson - Chemotherapy RDI and Cancer Survival (Completed)
Directory: /Users/lu/tehistark/mariner/applications/slr_v2/user_data/proj-004
UUID: proj-004

Run Settings

Chat Completion Model

gpt-3.5-turbo-0125 (context=16000k)

Full Text Enabled

Mode: Full Auto

Enable manual edits:

Data Constraints

Max articles to PRISMA: 50

Max articles to full-text PRISMA: 10

Max articles to Extract: 5

Performance & Utility

	Step 1: Protocol Development	Step 2: Search articles	Step 3: Screen articles	Step 4: Extract to tables	Efficiency Metrics
Full-Auto	<p>INCLUSION</p> <ul style="list-style-type: none"> Population: Studies must include patients diagnosed with secondary progressive multiple sclerosis (SPMS). Intervention: Studies must investigate the effects of Siponimod as a treatment. Outcome: Studies must report on clinical efficacy and/or safety outcomes of Siponimod treatment. <p>EXCLUSION</p> <ul style="list-style-type: none"> Non-human studies: Exclude studies that are not conducted on human subjects. Non-SPMS population: Exclude studies that do not focus on patients with secondary progressive multiple sclerosis. Other Interventions: Exclude studies that do not focus specifically on Siponimod as the intervention. 	<p>The query: 75-term query fully autonomously written by AI, optimised research question and protocol: 18 P-terms, 15 I-terms, 11 C-terms, 17 O-terms, 14 S-terms.</p> <p>Sources: PubMed</p> <p>Records returned: 85</p>	<p>Records identified: 85</p> <p>Input to TA: 85 Included by TA: 31 FT-s auto-obtained: 13 FT-included: 12 (disjoint with manual)</p> <p>Out of the included articles, 1 is a protocol (the inclusion exclusion criteria did not ask these to be exclude, 1 is in German - but the extraction still worked).</p>	<p>Data Extraction Accuracy (Full Auto):</p> <ul style="list-style-type: none"> 60% perfect match 33% partial match 7% requiring review Zero hallucinations 	<p>85 records → 12 studies</p> <p>5 minutes</p>
Part-Auto	<p>INCLUSION</p> <ul style="list-style-type: none"> Adult: The study population includes adults aged 18 years and older. SPMS: Patients are diagnosed with secondary progressive multiple sclerosis (SPMS). Intervention: The study must investigate at least one of the following interventions: <i>(list of 25 treatments including Siponimod)</i> Comparator: <i>(conditions on placebo, in 50 words)</i> Outcomes: The study must report any efficacy, health-related quality of life (HRQoL) or safety outcomes, including: <i>(plus 115 words more)</i> <p>• Study Design: The study design one of the following allowed types: (+70)</p> <p>• English: The abstract or full text is in English.</p> <p>EXCLUSION</p> <ul style="list-style-type: none"> Mixed Population: The study reports eligible outcomes in a mixed population, without separately reporting data for the population of interest (unless more than 80% of study population are adults with SPMS) Non-human: The study has non-human subjects. 	<p>The query: 69 part composite query written by the original study team: 6 I&P-terms, 32 S-terms, 30 I&C-terms.</p> <p>Sources: PubMed</p> <p>Records returned: 2715</p>	<p>Records identified: 2715</p> <p>Input to TA: 336 TA-included: 36 FT-s obtained: 25 FT-included: 17</p> <p>TA Recall = 0.92 FT recall = 0.90</p>	<p>Hybrid Performance:</p> <ul style="list-style-type: none"> 58% perfect match 35% partial match 8% poor match Zero hallucinations 	<p>2,715 records → 13 studies</p> <p>1 week</p>
Manual	<p>• Study Design: The study design one of the following allowed types: (+70)</p> <p>• English: The abstract or full text is in English.</p> <p>EXCLUSION</p> <ul style="list-style-type: none"> Mixed Population: The study reports eligible outcomes in a mixed population, without separately reporting data for the population of interest (unless more than 80% of study population are adults with SPMS) Non-human: The study has non-human subjects. 	<p>The query: Same as last row.</p> <p>Sources: PubMed + other</p> <p>Records returned: 3478 total (2726 from PubMed)</p>	<p>Records identified: 3478</p> <p>Input to TA: 3212 TA-included: 341 FT-s obtained: 341 FT-included: 97 (23 studies)</p>	<p>The AI discovered (1) page 55 NCT number wrong for ASCEND trial, (2) two cells that were missing from the original dossier draft IMPACT study on page 58.</p>	<p>3,478 records → 23 studies</p> <p>8 weeks</p>

Value

- First draft rapidly (5 minutes)
- Make better decisions for the rest
- Speed up the rest

Potential for Rare Diseases

- Patient Interviews
 - Automate interviews
- Data analysis
 - Rapid reviews and other reasoning across the 6000 diseases
- Regulatory documents
 - Produce them faster, at lower cost

Other?

Who are we at Tehistark



Dr. Meelis Lootus

CEO and Founder

PhD ML, University of Oxford VGG

- 13 years in AI + clinical research
- 5 start-ups, 2 acquisitions
- Senior ML Engineer @ doc.ai
- Director of AI Engineering @ Sharecare Inc



Dr. Lynn Gold

Chief Regulatory Advisor

PhD Organic Chemistry

- 35 years of leadership in the pharma industry
- 70 IND, 27 NDA, 6 ANDA, 2 BLA and 1 PMA
- VP Reg Affairs Impel Pharma



Lulu Beatson

Founding Engineer

BA Maths, University of Cambridge

- Co-authored papers on ML for digital biomarkers
- Developing ML pipelines
- Data & AI Engineer @ doc.ai
- Software Engineer @ RegGenome



Dr. Derek Driggs

Machine Learning Engineer

PhD ML, University of Cambridge

- Training AI systems to predict financial markets
- Published in top ML journals incl. Nature Machine Intelligence ([example SLR - Nature, cited by 783](#))



Kerry Hu

Research Assistant

MSci Neuro + MD student

- Validation Studies for in-house neurotechnology device @ HealthTech Connex
- Digital Biomarker Regulations Researcher at IEEE



Partner with Tehistark to Modernise your Workflows

meelis@tehistark.com

www.tehistark.com

