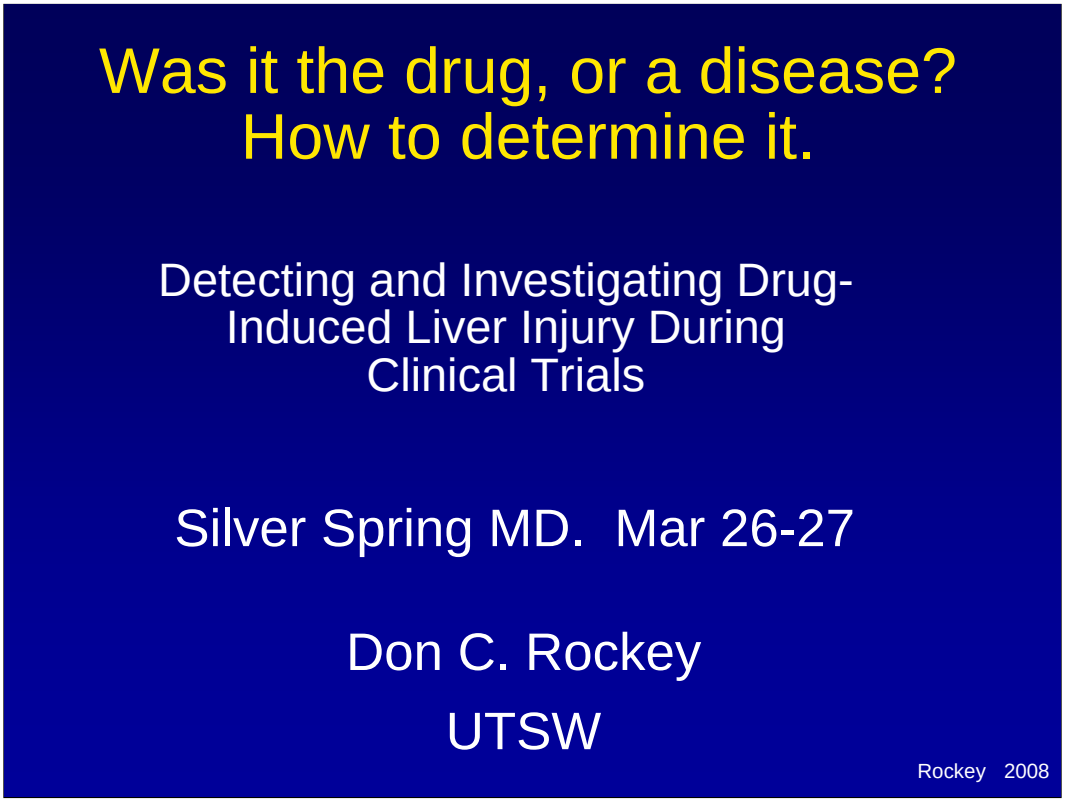


DR. WATKINS: Obviously the causality link links us right into our next talk. Okay. Don Rockey, University of Texas, Southwestern.

DR. ROCKEY: Thank you very much, Paul, and I, too, would like to start by thanking John Senior for the invitation and the opportunity to participate this morning. I've heard a lot of great material and it looks like the next day and a half will be fantastic as well.

John has asked me to talk about causality. Was it the drug or disease, and how do we determine this?

Overview

- Background - drug induced liver injury - what is it and why difficult diagnostically?
- Causality tools (instruments)
  - RUCAM
  - M & V Scale (CDS)
  - Expert opinion
- Drug Induced Liver Injury Network (DILIN) approach
- Summary/Future

Rockey 2008

I'm going to start with a little bit of background, about drug-induced liver injury and why it is diagnostically difficult. I'm going to talk about causality tools and instruments. I'm going to talk a little bit about RUCAM, the Maria and Victorino scale or the CDS scale, expert opinion. I'm going to spend most of the talk discussing the approach that the drug-induced liver injury network is using that you all have heard a little bit about, and then I'm going to wind up with some future predictions.

Background

Diagnostically difficult because

- Relatively common consideration
- Wide spectrum of disease
  - Clinical presentation
    - May “look” like almost any type of liver disease
  - Severity
    - Ranges from asymptomatic, to hospitalized, to death

Rockey 2008

Causality in drug-induced liver injury is difficult because the disease is actually hard to diagnose. As a clinician and diagnostician, this is tough. And the reason it's tough is because there is a very wide spectrum of disease and drug-induced liver injury can look like just about anything. It also is clear that there is a broad range as you just heard from Adrian in severity. Patients may be asymptomatic and have nothing more than abnormal aminotransferase or they may have fulminate hepatic failure and require transplantation or they can die.

Background

3 broad categories based on liver tests

Hepatocellular: R > 5 and ALT > 2x ULN or baseline

Cholestatic: R < 2 and Alk > ULN

Mixed: 2< R < 5

$$R = (ALT/ULN) / (Alk / ULN)$$

Rockey 2008

There are three broad categories of liver test abnormalities associated with DILI. Those include hepatocellular, so-called cholestatic and mixed, and these are clasically defined by the bar value which is essentially the ratio of the ALT, the upper limit of normal over the alkaline phosphatase.

Clinical Presentation

- Acute or chronic hepatitis
  - Autoimmune hepatitis
- Acute or chronic cholestasis
- Granulomatous disease
- Fibrosis / cirrhosis
- Fatty liver / NASH
- Sinusoidal obstruction syndrome
- Other

Rockey 2008

The clinical presentation can be one of acute or chronic hepatitis, can look like autoimmune hepatitis, and this becomes very difficult diagnostically particularly when you're not sure what the patient had or if you don't have baseline liver tests.

Acute or chronic cholestasis, granulomatous disease is a classic presentation for drug-induced liver injury and, of course, there are at least 100 other causes of granulomatous liver disease. Fibrosis and cirrhosis are relatively non-specific. There are a whole host of drugs that can cause fatty liver disease, sinusoidal obstruction syndrome caused by chemotherapeutic agents and, of course, there are many others as well.

Severity

- Mild liver injury - ALT < 2-3 X ULN (asyx)
- Symptomatic disease
- Severe liver injury - ALF, OLTx, death

Rockey 2008

Severity is also an issue in DILI. In most drug-induced liver injury it is mild and that's usually seen only in aminotransferases, but again patients can be symptomatic or have severe liver injury and even acute liver failure and death. These more severe patients are the ones that we see clinically.

Diagnostic Challenge

A diagnosis of exclusion (clinical evidence)

- Usually retrospective (timing often ?)
- Quality of data widely variable
- No lab test - one or panel
- Exclude other causes (must think of these)
- Requires a high index of suspicion
- Follow-up often required to confirm

Rockey 2008

I think the reason that DILI causation is really difficult is because essentially as Adrian mentioned in the previous talk, DILI is a diagnosis of exclusion. It usually occurs retrospectively and because the timing is so critical, retrospective analysis in DILI is problematic. And so if you don't have good history, it's very difficult to know the precise timing. The quality of the data is widely variable especially if you're asked to evaluate a patient retrospectively. There is no one lab test. For a lot of diseases that we care for, there is a laboratory test or a panel of tests that help us diagnostically. There isn't any such test here.

To exclude the other causes of liver disease, you have to think of these. Unfortunately to be good at this, you really have to have some expertise in hepatology or in the art of hepatology. And it requires a high index of suspicion and then follow up is always helpful but often not available. We're often left an incomplete data set and that is usually one of the biggest problems in causality.

Causality Instrument

- Simple to use, practical
- Generalizable to wide range of practioners
- Generalizable across types of cases
- Sensitive - high probability in drug cases
- Specific - low probability in non-drug cases
- Reproducible
- Quantitative or semi-quantitative
- High validity - evidence based and vs. expert

Rockey 2008

If we did have an ideal causality instrument or tool, what would it look like? Well, it should be simple to use. It should be practical. It should be generalizable to a wide range of practitioners. It should be generalizable across various types of drug-induced liver injury. It should obviously be sensitive and specific. It should be reproducible. It I think should be quantitative or semi-quantitative, and it should have a high degree of validity both evidence based and compared to an expert panel.

Causality Tools

- Expert opinion
- CIOMS Scale (or RUCAM)
- M & V Clinical Scale (or Clinical Diagnostic Scale - CDS)
- DILIN approach
- Other - Bayesian

Rockey 2008

The causality tools that I'm going to talk about are expert opinion, and we'll actually come back to that and talk about that in the DILIN approach. That's sort of what we all use now is expert opinion. Many of us are familiar with RUCAM and the Maria and Victorino scales. We'll talk a little bit about those now.

RUCAM

- Council for International Organizations of Medical Scientists (CIOMS) - recruited experts to develop a causality assessment tool for drug-induced liver disease
- France 1989 -- JP Benhamou (France), J Bircher (Germany), G Danan (France), WC Maddrey (US), J Neuberger (UK), F Orlandi (Italy), N Tygstrup (Denmark), HJ Zimmerman (US)
- Sponsored by Roussel Uclaf Pharmaceutical Company and called it “Roussel Uclaf Causality Assessment Method” or RUCAM

Danan and Benichou. J Clin Epidemiol 1993;46:1323 1330

Rockey 2008

RUCAM was or is a causality scale that was called for by the Council for International Organizations of Medical Scientists, and they recruited a variety of experts and you can see those here in the middle paragraph. This was a meeting that was sponsored by the Roussel Uclaf Pharmaceutical Company and therefore it's been called the Roussel Uclaf Causality Assessment Method or RUCAM for short.

RUCAM

1. Time to onset	(0 to 2)
2. Course	(-2 to 3)
3. Risk factors (ETOH/Age)	(0 to 2)
4. Concomitant drug(s)	(0 to -3)
5. Other causes	(-3 to 2)
6. Prior information on hepatox.	(0 to 2)
7. Response to readministration	(-2 to 3)

Score (-8 to 14)

Highly probable >8; Probable 6-8; Possible 3-5; Unlikely 1-2; Excluded ≤0

J Clin Epidemiol 1993;46:1323-1330 Rockey 2008

It contains seven different elements. The first two elements have to do with the timing and history of the onset of the clinical disease compared to when a patient began taking the drug. And again if you don't have a good history, this can be very difficult. There were two risk factors thrown into the mix, alcohol and age. The presence of alcohol or age over 55 are thought to be important. Concomitant drugs potentially responsible for DILI are considered in the RUCAM. Other causes, such as those you've heard about include hepatitis, hypertension, and whatnot.

Is there prior information on the hepatotoxicity of the drug? That's included in the RUCAM, and then a rechallenge or response to readministration, and one can develop a score anywhere from minus 8 to 14. There are 5 groups in the RUCAM, from highly probable, to probable, possible, unlikely and excluded.

RUCAM

- Advantages
  - Quantitative
  - Logical and carefully considered variables
- Disadvantages
  - Derived from expert opinion rather than prospectively collected data set
  - Cumbersome to use in practice
  - Uncommonly used by non-experts
  - Inflexible timing - e.g., hard to deal with delayed onset after drug d/c
  - ? Alcohol (presence or absence only)
  - Criteria for competing cause/drug not clear

Rockey 2008

The advantages of RUCAM are that it is quantitative. It's actually quite logical and I think that the expert panel that was assembled did a good job when they came up with the important variables. It's got some disadvantages though and that is that it was derived from just expert opinion and not from a prospectively collected data set. It is actually cumbersome to use in practice. It is used in many publications, but in a clinical practice, it's difficult. And I don't think it's ever used by non-experts.

It is a little bit inflexible in terms of the timing, and there are days that are included in it and patients have to fall within these dates to qualify for certain points. Alcohol was included. It was discussed whether alcohol was a risk factor truly or not, and then the criteria for competing causes or drugs is not entirely clear.

M & V Clinical Scale

Temporal Relationship - drug/clinical picture	
Time from initiation	(1 to 3)
Time from cessation	(-3 to 3)
Time to normalize	(0 to 3)
Alternative causes	(-3 to 3)
Extrahepatic manifestations	(0 to 3)
Reexposure	(0 to 3)
Previous reports	(-3 to 2)

Score (- 8 to 20)

Definite > 17; Probable 14-17; Possible 10-13; Unlikely 6-9; Excluded < 6

(Maria & Victorino Hepatology 1997;26: 664) Rockey 2008

The M&V Clinical Scale then is an extension of the RUCAM and was developed by a group in Portugal, and you can see, I'm not going to go through the various elements on this but there's heavy weighting towards the temporal relationship of the drug and clinical picture. Again, exclusion of alternative causes is important. The M & V scale also considers extrahepatic manifestations, reexposure or readministration and whether the drug been reported to previously cause liver injury.

M & V Clinical Scale

- 215 cases; 185 presumed drug-induced liver injury and 30 known to be due to an alternative cause of liver disease
- Compared with RUCAM
- Reviewed by 3 experts
- RUCAM better discriminative power
- RUCAM assessments closer to those of experts

Lucena et al. Hepatology 2001:33: 123

Rockey 2008

There is a data evaluating this instrument. This is a paper done by a Spanish group again, in which they took 215 cases, 185 of which were bona fide or presumed to be bona fide drug-induced liver injury cases and 30 known to be due to another type of liver disease and then compared this with RUCAM. All the cases were reviewed by three experts and they showed that the RUCAM actually had better discriminative power than the M&V scale. In addition, the RUCAM assessments were closer to those of the experts.

Drug-Induced Liver Injury Network: DILIN

A cooperative agreement funded by the Liver Disease Research Branch, NIDDK

Rockey 2008

Now, let me turn to the Drug-Induced Liver Injury Network or DILIN. As you know, this is a cooperative agreement that formed by the Liver Disease Branch at NIH, NIDDK, and funded by NIH.

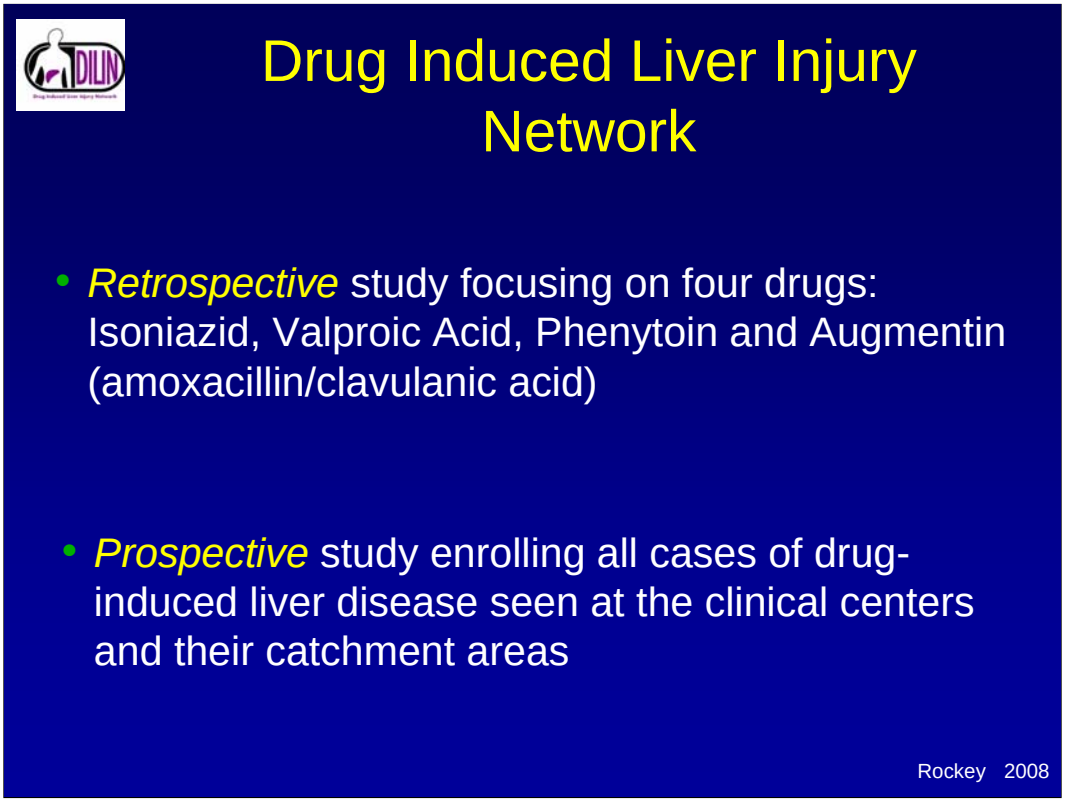
Drug-Induced Liver Disease Network (DILIN): Overall Objectives

- To provide a database containing carefully phenotyped cases of hepatotoxicity
- To develop standardized definitions, grading systems and clinical instruments to identify and assign causality to cases of suspected drug-induced liver injury
- To obtain biological samples for studies on the pathogenesis of hepatotoxicity using biochemical, molecular, immunologic and genetic techniques

Rockey 2008

Its overall, overarching objectives are to provide a database containing carefully phenotyped cases of hepatotoxicity, to develop standardized definitions, grading systems and clinical instruments to identify and assign causality to cases of suspected drug-induced liver injury and to obtain biological samples for future study.

Many of the investigators are here in the audience and a number of people from the NIH and FDA are also involved and are also present. I personally am a little bit biased here. Much has been learned and much has been accomplished already and it's just gone out for a recompetition and so we'll see how that goes but I think that it's just getting started, and this is going to turn into a wonderful project.



There are two recruiting wings of this study. One is a retrospective study and one is a prospective study. The retrospective study focuses on four drugs, and this is really Paul's brain child. The prospective study is enrolling all cases of drug-induced liver injury seen in clinical settings.

DILIN Prospective study

- Inclusion criteria
  - Liver injury due to a drug or CAM within 6 months of presentation
  - On 2 consecutive blood draws
    - AST / ALT > 5 X ULN or baseline
    - Alk phos > 2X ULN or baseline
    - T bilirubin > 2.5 mg/dl
- Exclusion criteria
  - Acetaminophen hepatotoxicity
  - Pre-existing AIH, PSC / PBC, OLT

Rockey 2008

I'm going to talk just about the prospective study from now on; the inclusion criteria for this study are liver injury due to a drug or alternative medication within six months of presentation, and on two separate occasions patients have to have aminotransferase five times greater than the upper limit of normal or baseline, alk phos twofold elevated or a total bilirubin of 2.5. There was a lot of discussion about whether these were the most appropriate criteria or not but this is ultimately what was decided upon. The exclusion criteria are obvious acetaminophen hepatotoxicity or preexisting conditions shown here.

Causality Assessment

A critical issue in drug induced liver injury is accurate causality assessment

Rockey 2008

Now this is what happens when you use an Apple MacIntosh. So that was actually a cartoon trying to emphasize how important the causality assessment is in drug-induced liver injury, and I think that this is, you know, it's obviously the critical issue here. If we don't have good causality assessment cases we don't have a way forward.

DILIN Protocol for Evaluation
(Prospective)

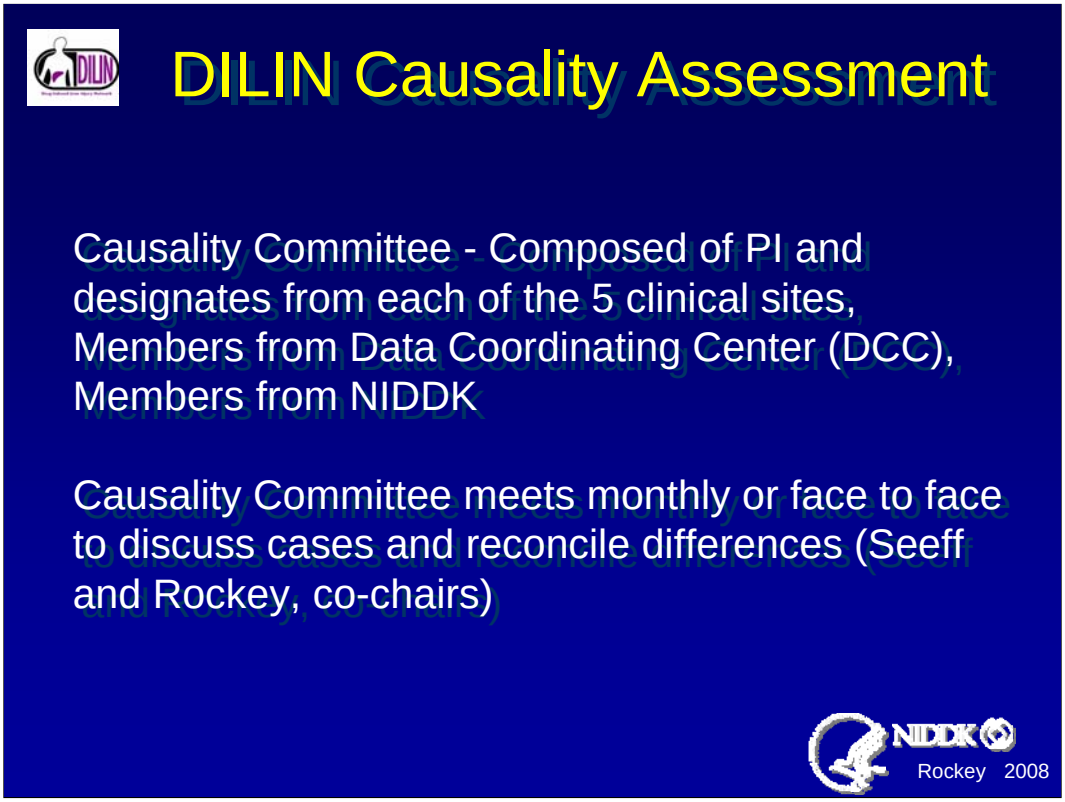
- Cases are identified by site investigators
- Each case is evaluated in a standard, formalized fashion with collection of medical history and all laboratory test results (extensive CRFs)

  (Serum, urine, PBMC and DNA are obtained from each patient & sent to NIDDK repository)
- Each case is evaluated by 3 experts to establish an assessment of causality

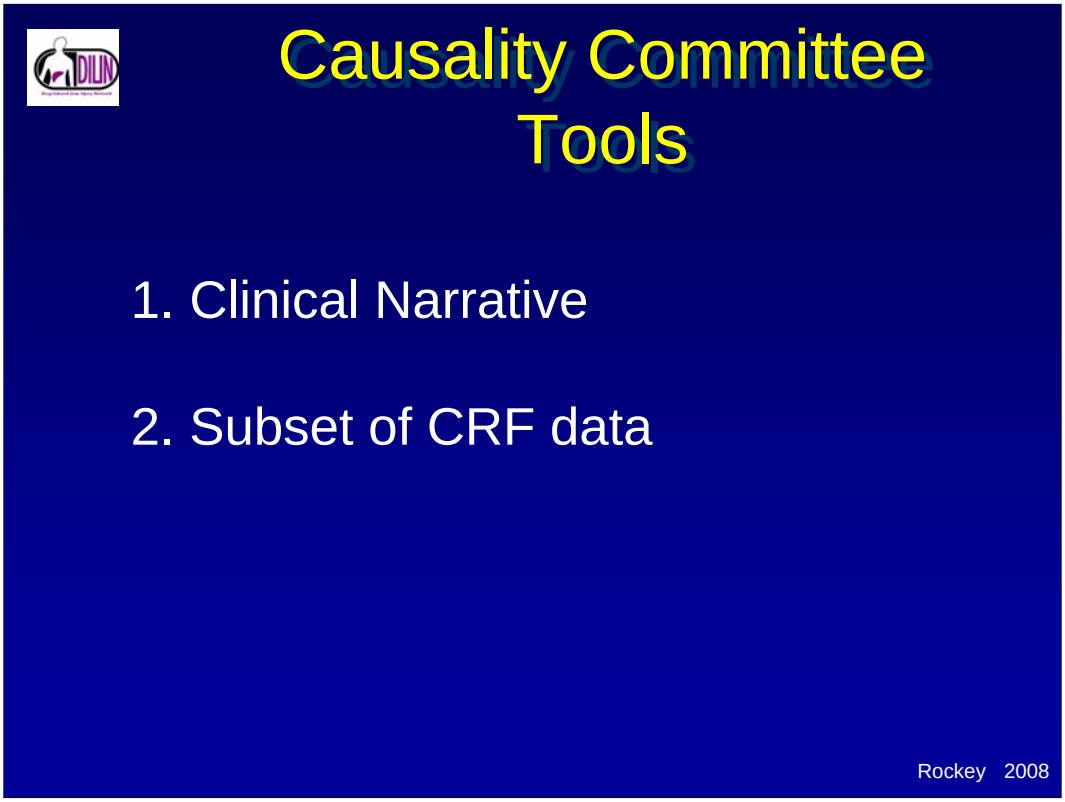
(At least six-month follow up is obtained)

Rockey 2008

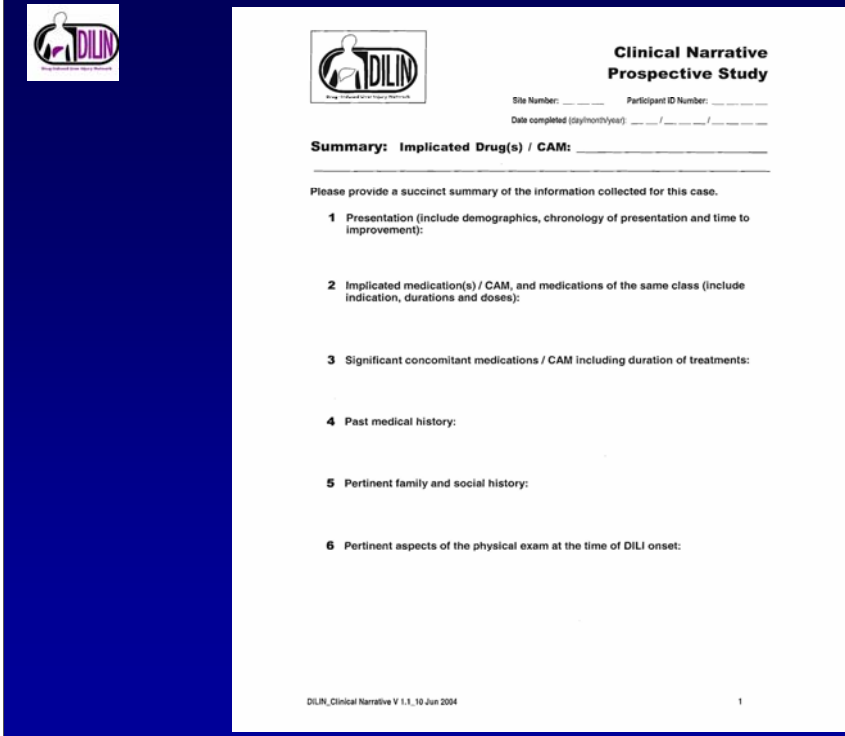
The way this works is that cases are identified by the five site investigators. Each case is evaluated in a standard, formalized fashion with a collection of extensive medical history and laboratory tests. The CRF I think is 47 pages. It's quite extensive, and then specimens are collected as well and deposited in the NIDDK repository. Each case is evaluated by three experts to establish causality.



And the way we establish causality is by a committee approach. The committee is composed of each of the five PIs and several of their designees (from the five clinical sites), members of the coordinating center including myself and NIDDK, including Leonard Seeff, Jay Hoofnagle, and Jose Serrano. We meet monthly or at face-to-face meetings to discuss and reconcile differences.



We have developed a number of tools and again this required a lot of work as well.



Clinical Narrative
Prospective Study

Site Number: __ __ __ Participant ID Number: __ __ __ __

Date completed (day/month/year): __ __ / __ __ __ / __ __ __ __

Summary: Implicated Drug(s) / CAM: _____

Please provide a succinct summary of the information collected for this case.

1 Presentation (include demographics, chronology of presentation and time to improvement):

2 Implicated medication(s) / CAM, and medications of the same class (include indication, durations and doses):

3 Significant concomitant medications / CAM including duration of treatments:

4 Past medical history:

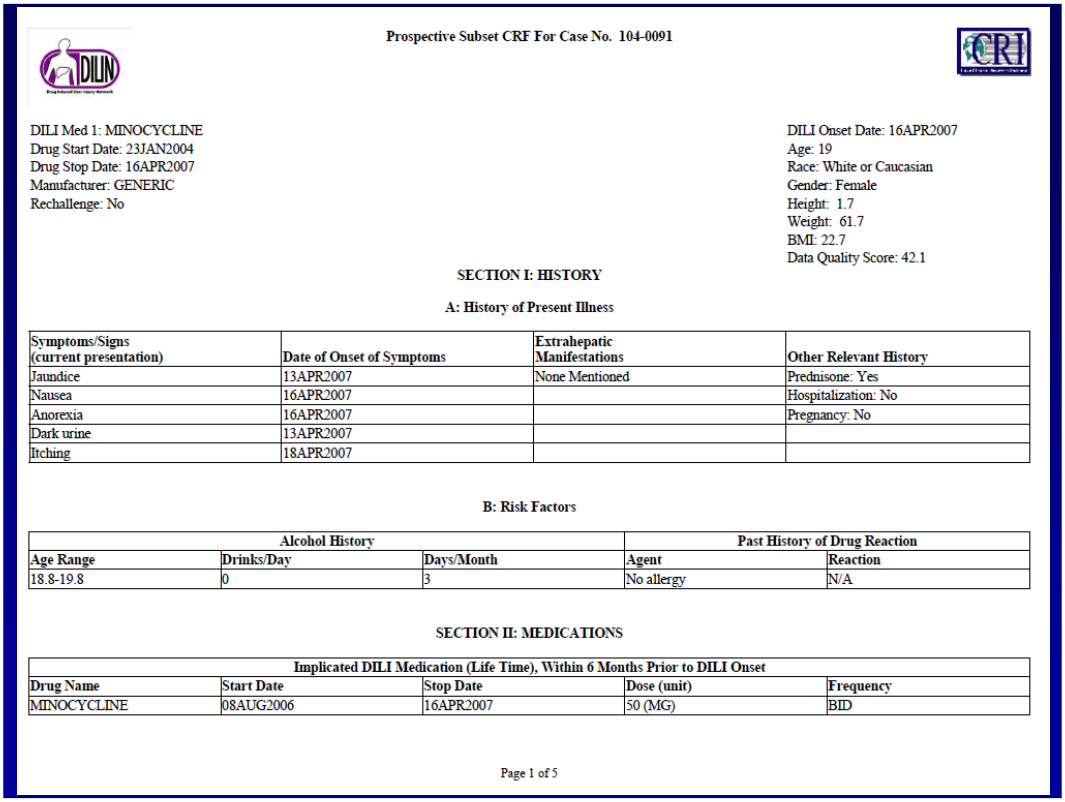
5 Pertinent family and social history:

6 Pertinent aspects of the physical exam at the time of DILI onset:

DILIN_Clinical Narrative V 1.1_10 Jun 2004 1

Rockey 2008

This is a form that everybody fills out that describes in a narrative fashion the patient.



Prospective Subset CRF For Case No. 104-0091

DILI Med 1: MINOCYCLINE
Drug Start Date: 23JAN2004
Drug Stop Date: 16APR2007
Manufacturer: GENERIC
Rechallenge: No

DILI Onset Date: 16APR2007
Age: 19
Race: White or Caucasian
Gender: Female
Height: 1.7
Weight: 61.7
BMI: 22.7
Data Quality Score: 42.1

SECTION I: HISTORY

A: History of Present Illness

Symptoms/Signs (current presentation)	Date of Onset of Symptoms	Extrahepatic Manifestations	Other Relevant History
Jaundice	13APR2007	None Mentioned	Prednisone: Yes
Nausea	16APR2007		Hospitalization: No
Anorexia	16APR2007		Pregnancy: No
Dark urine	13APR2007		
Itching	18APR2007		

B: Risk Factors

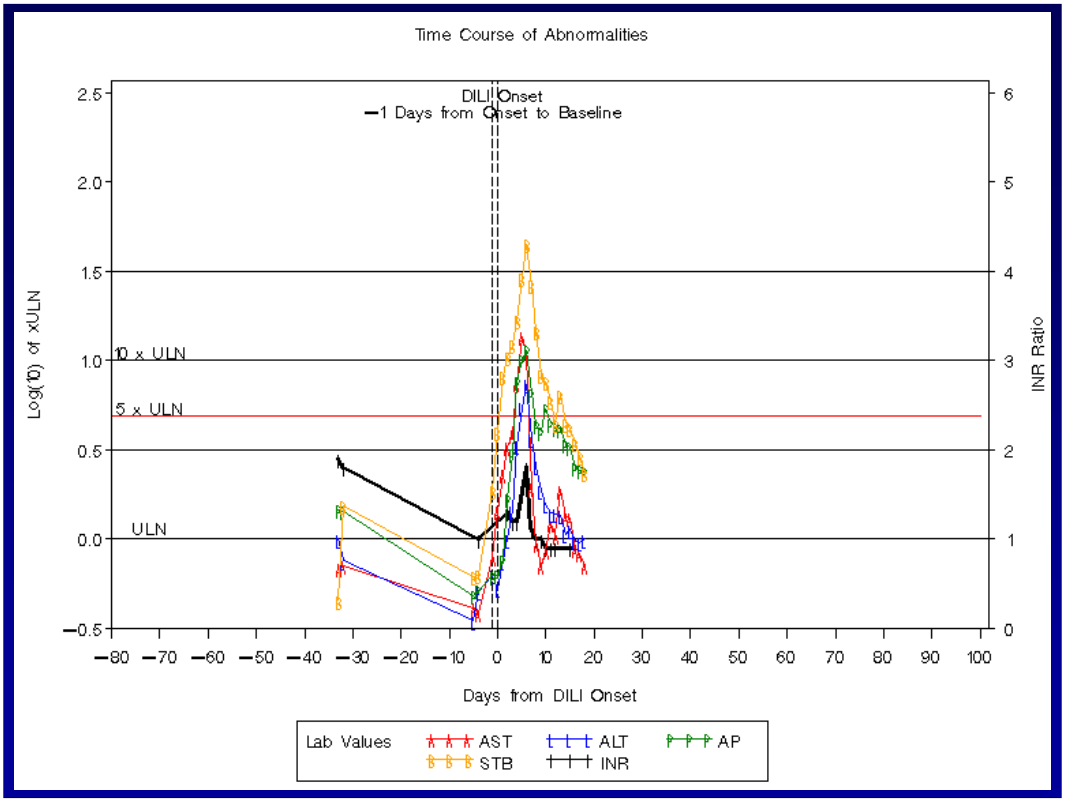
Alcohol History			Past History of Drug Reaction	
Age Range	Drinks/Day	Days/Month	Agent	Reaction
18.8-19.8	0	3	No allergy	N/A

SECTION II: MEDICATIONS

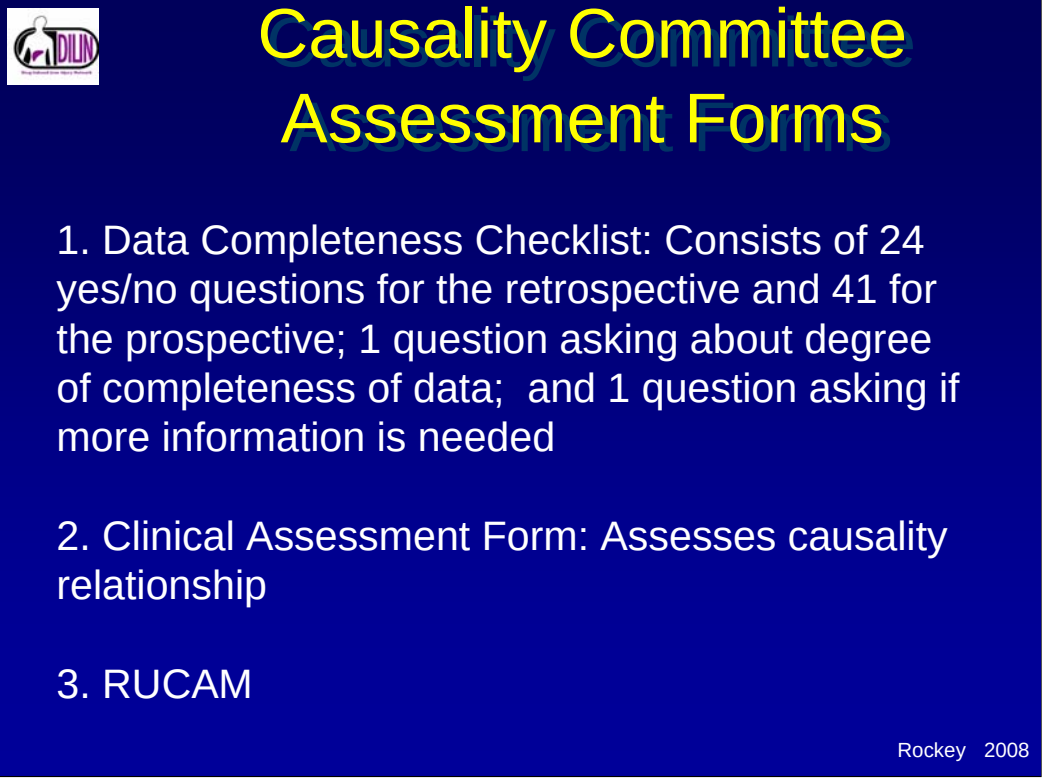
Implicated DILI Medication (Life Time), Within 6 Months Prior to DILI Onset				
Drug Name	Start Date	Stop Date	Dose (unit)	Frequency
MINOCYCLINE	08AUG2006	16APR2007	50 (MG)	BID

Page 1 of 5

This is an example of the subset CRF. So this again is a subset of this gigantic CRF that contains what we view to be the absolutely critical elements. You can see demographic data is included here, the historical data, previous medications, past medical history and then we go through all the laboratories and other diagnostic tests.



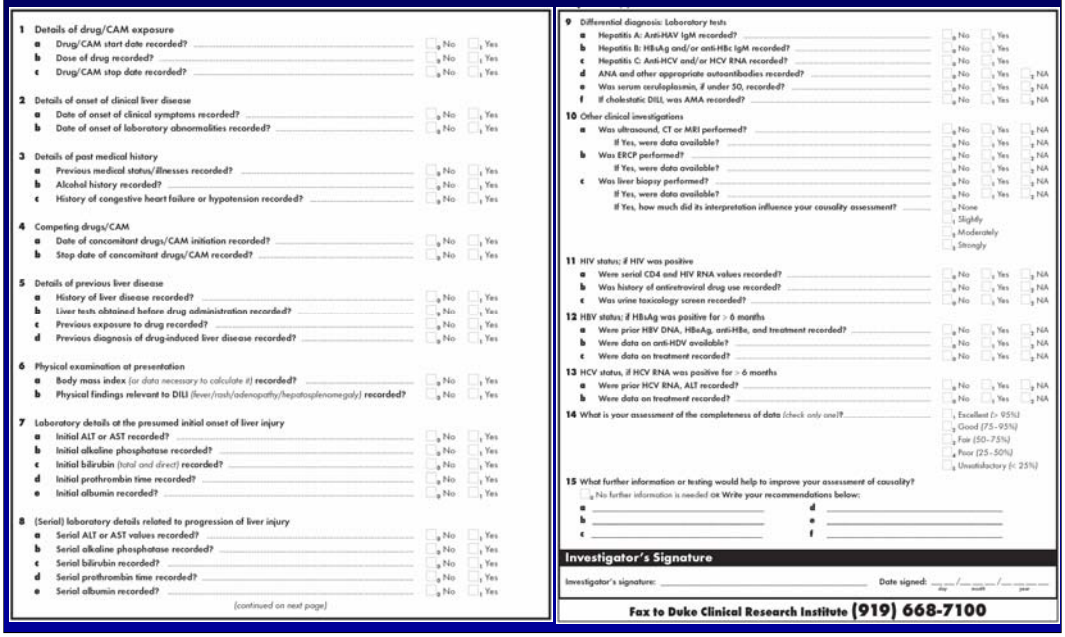
There even is a cute little graph that is included that plots the laboratory test abnormalities. This is an example of that.



Thus, we have a lot of tools available to do the assessments. Committee members are then required to fill out several forms. When we initially started, we had a fairly extensive data completeness checklist. We wanted to make sure that we had perfect data on everybody. This was actually done by hand initially, but is now done by computer. Once the data is reviewed, reviewers complete a clinical assessment form that reports a causality score and each member completes a RUCAM form on each case.

Causality Tools

Quality sheet



1 Details of drug/CAM exposure
- a Drug/CAM start date recorded? ... 0 No 1 Yes
- b Dose of drug recorded? ... 0 No 1 Yes
- c Drug/CAM stop date recorded? ... 0 No 1 Yes

2 Details of onset of clinical liver disease
- a Date of onset of clinical symptoms recorded? ... 0 No 1 Yes
- b Date of onset of laboratory abnormalities recorded? ... 0 No 1 Yes

3 Details of past medical history
- a Previous medical status/illnesses recorded? ... 0 No 1 Yes
- b Alcohol history recorded? ... 0 No 1 Yes
- c History of congestive heart failure or hypotension recorded? ... 0 No 1 Yes

4 Competing drugs/CAM
- a Date of concomitant drugs/CAM initiation recorded? ... 0 No 1 Yes
- b Stop date of concomitant drugs/CAM recorded? ... 0 No 1 Yes

5 Details of previous liver disease
- a History of liver disease recorded? ... 0 No 1 Yes
- b Liver tests obtained before drug administration recorded? ... 0 No 1 Yes
- c Previous exposure to drug recorded? ... 0 No 1 Yes
- d Previous diagnosis of drug-induced liver disease recorded? ... 0 No 1 Yes

6 Physical examination at presentation
- a Body mass index *(or data necessary to calculate it)* recorded? ... 0 No 1 Yes
- b Physical findings relevant to DILI *(fever/rash/adenopathy/hepatosplenomegaly)* recorded? ... 0 No 1 Yes

7 Laboratory details at the presumed initial onset of liver injury
- a Initial ALT or AST recorded? ... 0 No 1 Yes
- b Initial alkaline phosphatase recorded? ... 0 No 1 Yes
- c Initial bilirubin *(total and direct)* recorded? ... 0 No 1 Yes
- d Initial prothrombin time recorded? ... 0 No 1 Yes
- e Initial albumin recorded? ... 0 No 1 Yes

8 (Serial) laboratory details related to progression of liver injury
- a Serial ALT or AST values recorded? ... 0 No 1 Yes
- b Serial alkaline phosphatase recorded? ... 0 No 1 Yes
- c Serial bilirubin recorded? ... 0 No 1 Yes
- d Serial prothrombin time recorded? ... 0 No 1 Yes
- e Serial albumin recorded? ... 0 No 1 Yes

(continued on next page)

9 Differential diagnosis: Laboratory tests
- a Hepatitis A: Anti-HAV IgM recorded? ... 0 No 1 Yes
- b Hepatitis B: HBsAg and/or anti-HBc IgM recorded? ... 0 No 1 Yes
- c Hepatitis C: Anti-HCV and/or HCV RNA recorded? ... 0 No 1 Yes
- d ANA and other appropriate autoantibodies recorded? ... 0 No 1 Yes 9 NA
- e Was serum ceruloplasmin, if under 50, recorded? ... 0 No 1 Yes 9 NA
- f If cholestatic DILI, was AMA recorded? ... 0 No 1 Yes 9 NA

10 Other clinical investigations
- a Was ultrasound, CT or MRI performed? ... 0 No 1 Yes 9 NA
  - If Yes, were data available? ... 0 No 1 Yes 9 NA
- b Was ERCP performed? ... 0 No 1 Yes 9 NA
  - If Yes, were data available? ... 0 No 1 Yes 9 NA
- c Was liver biopsy performed? ... 0 No 1 Yes 9 NA
  - If Yes, were data available? ... 0 No 1 Yes 9 NA
  - If Yes, how much did its interpretation influence your causality assessment? ... 0 None 1 Slightly 2 Moderately 3 Strongly

11 HIV status; if HIV was positive
- a Were serial CD4 and HIV RNA values recorded? ... 0 No 1 Yes 9 NA
- b Was history of antiretroviral drug use recorded? ... 0 No 1 Yes 9 NA
- c Was urine toxicology screen recorded? ... 0 No 1 Yes 9 NA

12 HBV status; if HBsAg was positive for > 6 months
- a Were prior HBV DNA, HBeAg, anti-HBe, and treatment recorded? ... 0 No 1 Yes 9 NA
- b Were data on anti-HDV available? ... 0 No 1 Yes 9 NA
- c Were data on treatment recorded? ... 0 No 1 Yes 9 NA

13 HCV status, if HCV RNA was positive for > 6 months
- a Were prior HCV RNA, ALT recorded? ... 0 No 1 Yes 9 NA
- b Were data on treatment recorded? ... 0 No 1 Yes 9 NA

14 What is your assessment of the completeness of data *(check only one)*? ... 1 Excellent (> 95%) 2 Good (75–95%) 3 Fair (50–75%) 4 Poor (25–50%) 5 Unsatisfactory (< 25%)

15 What further information or testing would help to improve your assessment of causality?
0 No further information is needed OR Write your recommendations below:
- a ____ d ____
- b ____ e ____
- c ____ f ____

Investigator's Signature

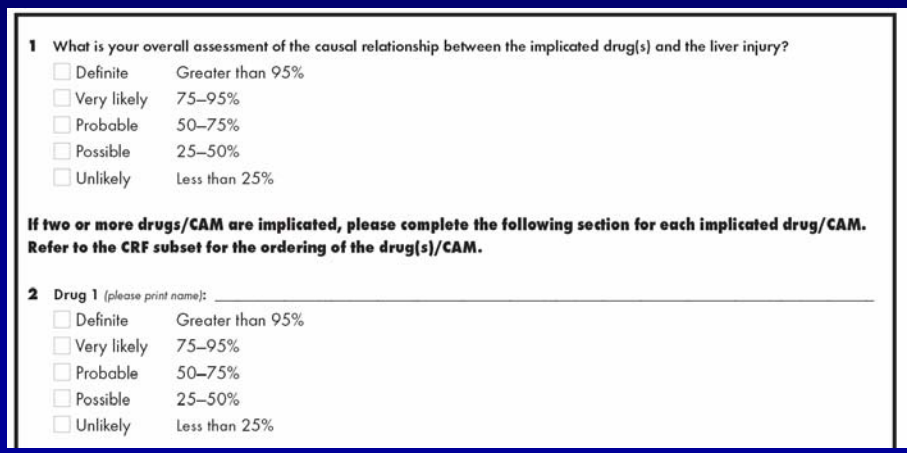
Investigator's signature: ____ Date signed: ____/____/____ (day / month / year)

Fax to Duke Clinical Research Institute (919) 668-7100

This is the data quality sheet. You can see here that this is fairly extensive and this excludes all kinds of what you would think to be obviously parameters, if the patient has hepatitis A or B or C, hypertension shock, what have you.

Causality Tools

Scoring system



1 What is your overall assessment of the causal relationship between the implicated drug(s) and the liver injury?

☐ Definite	Greater than 95%
☐ Very likely	75–95%
☐ Probable	50–75%
☐ Possible	25–50%
☐ Unlikely	Less than 25%

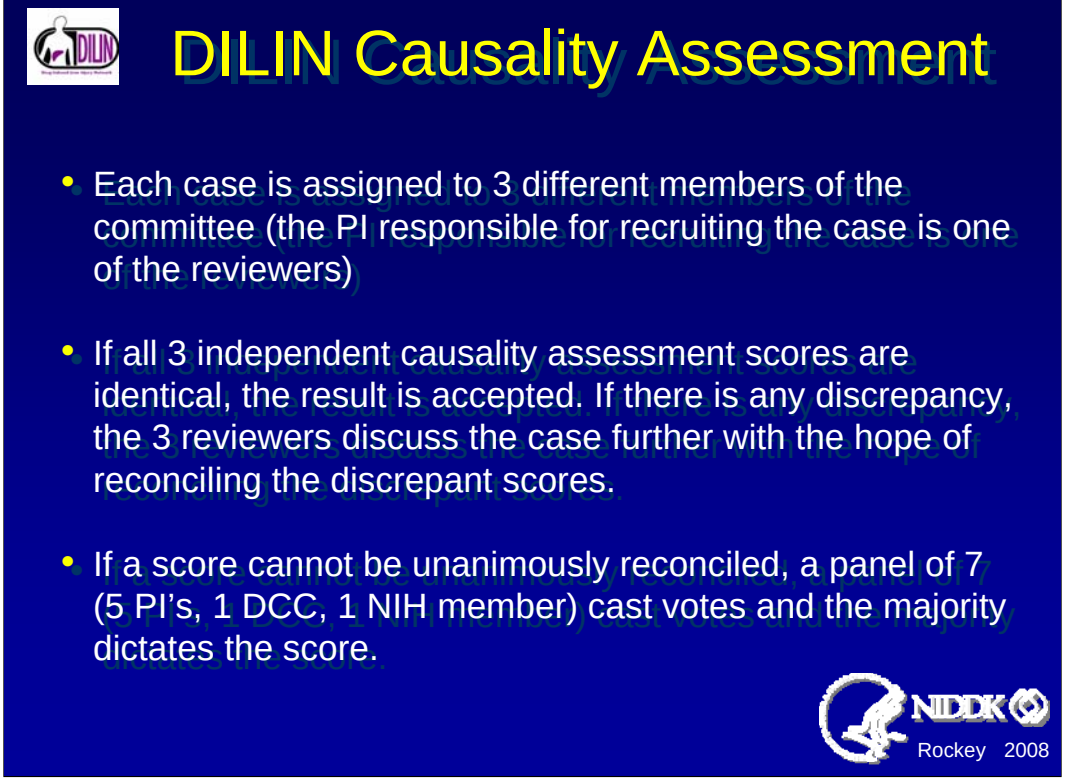
If two or more drugs/CAM are implicated, please complete the following section for each implicated drug/CAM. Refer to the CRF subset for the ordering of the drug(s)/CAM.

2 **Drug 1** *(please print name)*: _____

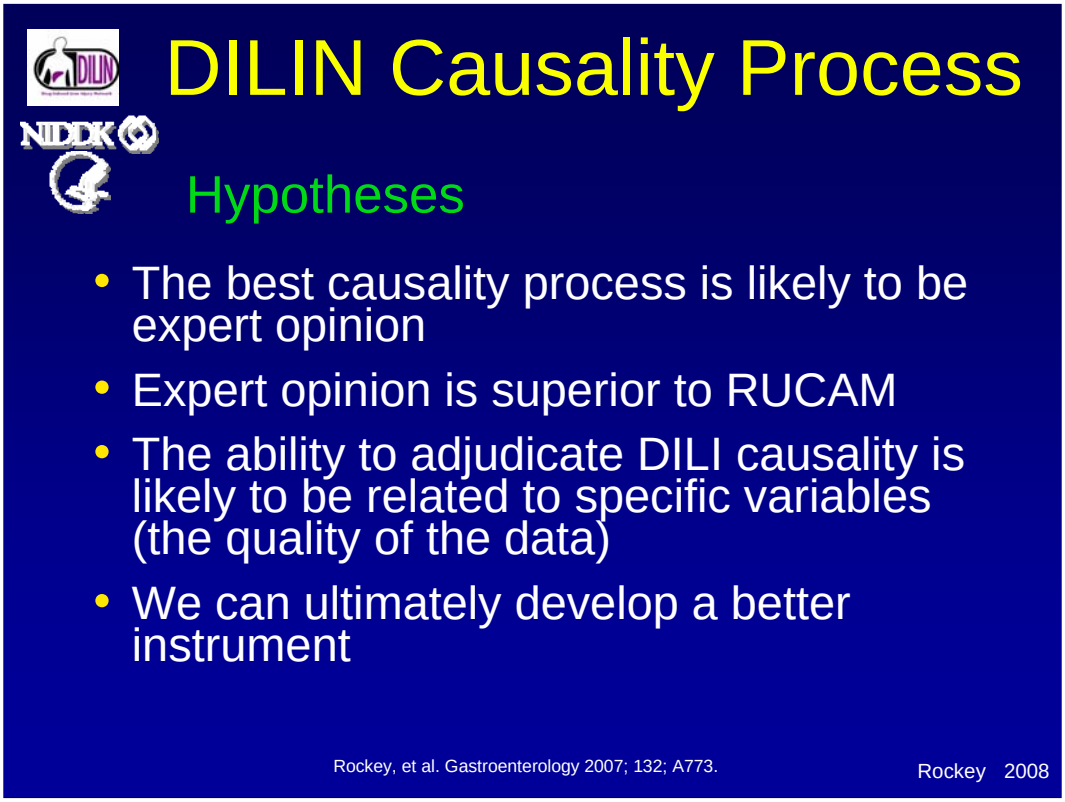
☐ Definite	Greater than 95%
☐ Very likely	75–95%
☐ Probable	50–75%
☐ Possible	25–50%
☐ Unlikely	Less than 25%

Rockey 2008

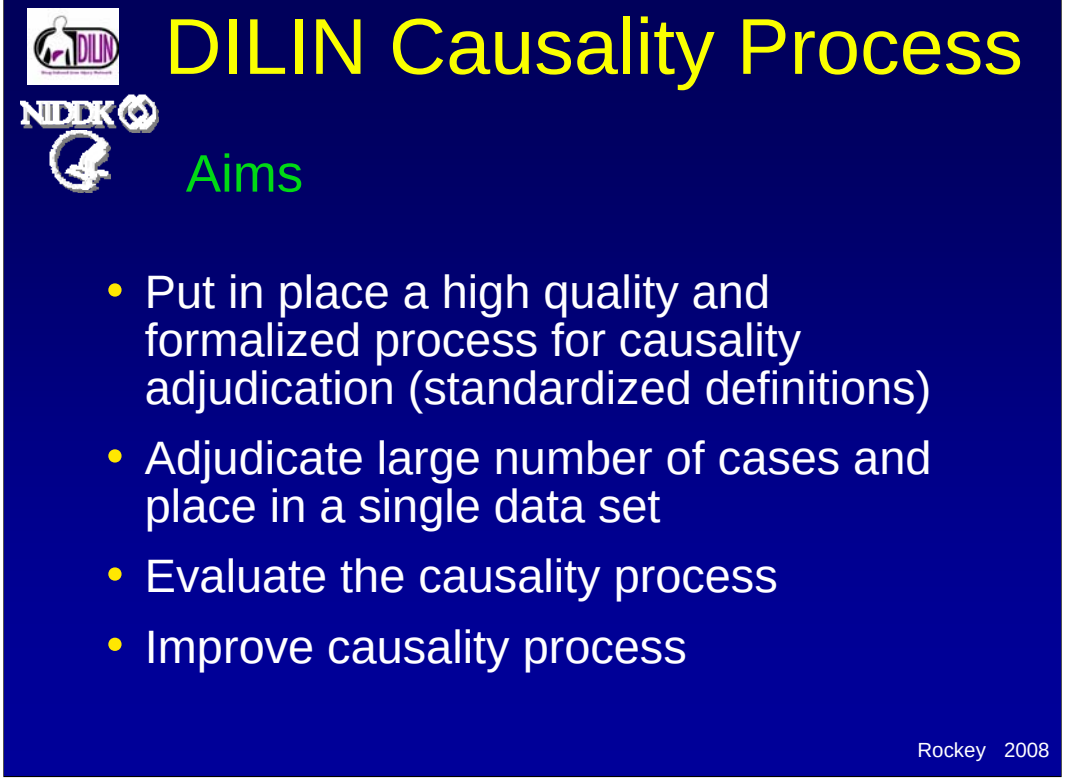
This is the scoring system. We use a five point scoring system from definite to very likely, probable, possible and unlikely. We have assigned a percent likelihood to each one of these categories. We do an overall assessment for the overall case and when we have multiple drugs, we do assessments for each of the top three candidates.



Each case is assigned to three different members of the committee. The PI responsible for recruiting the cases is automatically one of the reviewers. If all three of the independent assessment scores are identical, then we accept the result as final. If there's any discrepancy amongst the reviewers, then this has to be adjudicated and this is discussed at the time of our conference call. If a score cannot be agreed upon, and this does not happen infrequently, then we take a vote. There are seven voting members and we take the majority vote then as the final score.



We've had a couple of ideas moving forward with regard to the causality process and I'm just going to throw a couple of these hypotheses out. This was actually presented last year at DDW. We thought that the best causality process is likely to be expert opinion. Further, we postulated that expert opinion would be superior to RUCAM. Additionally, the ability to adjudicate causality is likely to be related to specific variables. We actually are not sure what those variables are. One of those may be the quality of the data. And we also believe that we can ultimately develop a better instrument or a better process.



Our aims were to put in place a high quality and formalized process for causality and adjudication and if I don't emphasize anything else, I hope I've emphasize the rigor in which this is done. So this was very carefully thought out and it's an extremely rigorous process.
e have adjudicated a large number of cases and placed these in a single data set. So far we have completed 250 cases.. We would like to evaluate the causality process and then ultimately improve it.

Summary

- Better agreement in initial causality with expert opinion than with RUCAM, particularly higher scoring cases
- RUCAM underestimates drug - injury association
- Expert opinion exhibits less variability than RUCAM, also in higher scoring cases
- Is expert opinion truly better than RUCAM?
- Expert opinion is clearly not perfect - requires standardization of terms and definitions

Rockey 2008

To summarize then, what we found or reported is that there is better agreement in the initial causality score with expert opinion than with RUCAM particularly in the higher scoring cases. The RUCAM tends to underestimate the drug and injury association at least in this series of cases. Expert opinion is less variable than RUCAM overall and is clearly less variable in the higher scoring cases. So is expert opinion better than RUCAM? Well, I don't know. Expert opinion clearly is not perfect and I think this is going to require a lot more work. It certainly is not generalizable. There aren't that many people that could actually do what we do. It clearly is going require standardization in terms and definitions.

Future

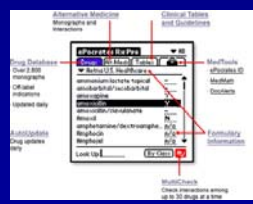
- Can we identify the variables that lead to agreement or disagreement?
- Can we use these data/approach to develop a more generalizable tool?
- Quantitative approach?

Rockey 2008

So where is this going in the future? Well, I've thrown out a couple of questions here. Can we identify the variables that lead to agreement or disagreement? I mean I think that would be a critical question to figure out why we agree or disagree. Can we use the data that we've got now to develop a more generalizable tool? Which I think would be very important to advance it if we could. Can we develop something that's quantitative and let's say is better than RUCAM? What's going to happen? You know, this was a guy pondering a diagnosis of drug-induced liver injury.

Causality Assessment circa 2020

- Patient will become ill with suspected drug induced liver injury
- Computer based search/algorithm
- Causality score provided (?MELD)



Rockey 2008

But what I would love to see is something like this. A patient gets sick with suspected drug-induced liver injury. As a clinician, you identify the drug, potential culprit. You then go to your computer or your handheld device here. And you use a computer based search or algorithm that asks you for certain data. You provide the data and then you get a causality score, telling you how likely is your patient to have drug-induced liver injury.

This reminds me a lot of MELD. You can just go in, plug in three numbers and boom, you have a number and we're good to go.

So this is where I hope the field is going to go and that is my last slide.