Preliminary Testing of a Database for Patient Level Assessment of Drug-Induced Liver Injury in Drug Development (PLADD)

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Abstract

Background/Purpose: Drug-induced liver injury (DILI) assessment requires patient level analysis. Our objective was to create a Patient Level Assessment Database for DILI (PLADD) that would increase efficiency and consistency.

Methods: A PLADD was developed using Access® and tested for manual upload of data using 44 DILI cases from an IND and LiverTox®. Assessment of accuracy and ease of data entry for these cases was used to hone PLADD structure. Multiple automatically calculated (e.g., time from drug start to injury, time to recovery) and searchable free text fields were embedded. Queries were created for summary statistics for all cases and subgroups. PLADD was then applied to 36 cases of potential DILI in 2 separate INDs. A trainee without expertise in DILI initially read each case and filled in data fields. A physician with expertise in DILI independently checked each entry for accuracy. After corrections, the physician used PLADD to adjudicate DILI likelihood on a scale of 1 to 5, where 1 is definite DILI and 5 is unlikely.

Results: In IND 1, PLADD summaries found significant differences between DILI in heathy volunteers (HV) versus patients, that were unrecognized in 2 prior DILI consults. Patients with DILI had a median age 27 years older than HVs with DILI (58 vs. 31 yr.). A cholestatic DILI was noted in patients but was not seen in HVs. In IND 2, PLADD showed a narrow latency (mean 44.6 days, SD 10.6) and a 12.5% chronicity rate. Both findings were important to a partial clinical hold decision. The trainee's data entry was approximately 95% correct; inaccuracies stemmed from need for expert input (e.g., defining date of DILI onset) and misinterpretation of medical terms before data entry. PLADD saved the physician approximately 2 work hours/consult.

Conclusions: PLADD may improve assessments by supplying a searchable computerized case form and summary statistics for identification of trends and outliers, which might otherwise go unnoticed. DILI expertise is not needed for data entry but is needed to ensure data accuracy and for case adjudication. PLADD will be tested by other physicians for further refinement and then for automatic upload of NDA data, obviating manual entry.

Introduction

- Drug Induced Liver Injury (DILI) remains a significant challenge in drug development.
- Case level assessment by medical officers in the Division of Hepatology and Nutrition (DHN) is time consuming but necessary for risk assessment in BLAs and NDAs.
- Lack of a structured, case level DILI assessment tool in DHN may lead to inconsistencies and overlooked data in DILI consultations.

Aim

Our aim was to developed a searchable database for case level data entry, note taking and DILI assessment.

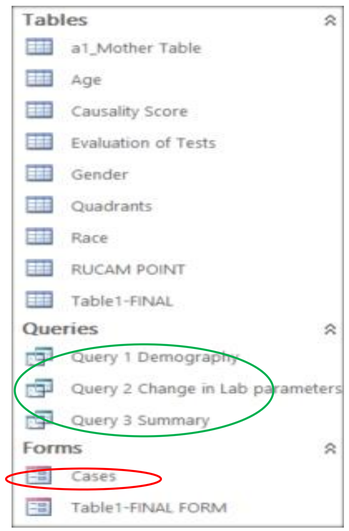
Materials and Methods

- Access® was used to develop the Patient Level Assessment Database for DILI (PLADD).
- Initial testing and modifications were done by manual data entry of 44 cases from LiverTox® and two active INDs with DILI safety concerns.
- Access ® queries were embedded to summarize commonly needed DILI parameters (e.g., latency, peak liver enzymes, age, R-values).
- 36 potential DILI cases from 2 INDs were assessed using PLADD.
- Each case narrative was read, and data were uploaded by an ORISE Fellow (ECV) who had no prior expertise in DILI.
- Data entry was then verified by a medical officer (PHH) with expertise in DILI.
- This medical officer then used PLADD to diagnose DILI likelihood using the DILI Network likelihood scale for 1 to 5 with 1 being definite and 5 being unlikely.
- Several automatically calculated field were embedded including latency and washout times based on entered date field. R-values at DILI onset and peak were also automatically calculate based on lab and upper limit of normal entry.

Results and Discussion

Medical officers are expected to use the Cases Form (red oval) to do their assessments case-by-case. (See Figure 1) Data would be pre-entered for them. Medical officers can then use the standard Queries (green oval) to look for trends or similarities between cases. Queries are easily exported to Excel for summary statistics (e.g., mean age, mean latency, mean ALT value) and graphing.

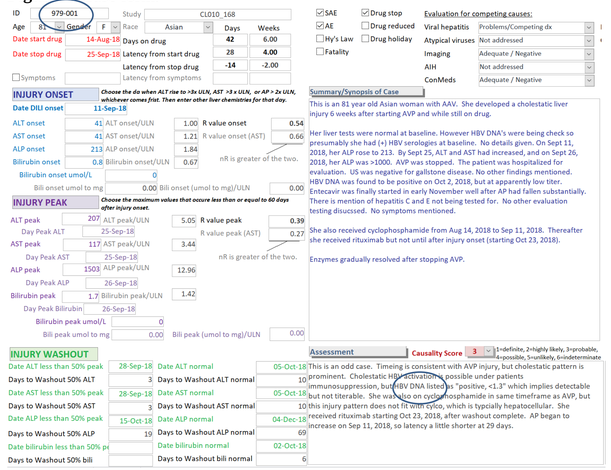
Figure 1: Menu of Tables, Queries and Forms.



Results and Discussion (continued)

Lab values and date fields pre-populated by the ORISE Fellow but other fields (e.g., R-value) calculated by the computer. (Figure 2) Medical officer checked data and then wrote Summary, Assessment and score. Notes & Alternate Diagnosis fields are on the form but not shown. Cases can be filtered text as needed. For example, the case shown may be found by searching all cases for Case ID "979-001" or by the string "DNA" in the Assessment field. (blue ovals)

Figure 2: Case form.



Query 3 filtered on *healthy volunteers* with at least possible DILI (Causality Score ≤ 4). Median age of 31(blue oval) significantly lower than for patients (Tables 1 vs. 2). No cholestatic volunteers as indicated by all R-values > 2.0 (blue box).

Table 1. Query 3 tabular data from DILI consult IND-1—Healthy Volunteers

ID	Causality Score	Age	Gender	Hy's Law	Latency from start drug (da.)	Latency from stop drug	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak
01-13-17-043	3	25	M	FALSE	18	8	590	518	416	2.4	4.10
01-13-17-023	3	27	F	FALSE	18	8	158	108	130	1.2	3.51
01-13-17-011	3	19	M	FALSE	18	8	180	162	130	1.2	4.00
01-13-17-003	3	35	F	FALSE	18	8	518	270	130	1.2	11.51
01-06-16-039	2	26	F	FALSE	16	0	2430	1170	390	1.2	18.00
01-14-012	3	53	M	FALSE	36	10	292	112	130	1.2	6.49
01-14-001	3	50	F	FALSE	28	2	153	108	156	1.2	2.83
01-05-15-022	3	30	M	FALSE	16	12	144	108	130	1.2	3.20
01-06-16-038	3	32	F	FALSE	18	0	221	90	130	1.2	4.91
01-06-16-030	2	41	M	FALSE	17	0	450	414	234	1.2	5.56
01-06-16-013	3	20	F	FALSE	24	10	144	45	130	1.2	3.20
01-02-14-4005	4	23	M	FALSE	20	15	171	45	143	1.2	3.45
01-13-17-002	3	30	F	FALSE	18	8	194	135	130	1.2	4.31
01-13-17-001	3	39	F	FALSE	18	8	216	158	130	1.2	4.80
01-07-16-214	3	32	F	FALSE	20	10	194	144	130	1.2	4.31
01-07-16-201	3	34	M	FALSE	20	10	162	81	130	1.2	3.60
01-06-16-029	4	35	M	FALSE	19	18	405	315	130	1.2	9.00
01-06-16-017	3	35	M	FALSE	34	5	140	90	130	1.2	3.11
Median	**3**	**31**	9 F	0 Hy's Law	**18.00**	**8.00**	**194.00**	**123.50**	**130.00**	**1.20**	**4.20**
Max	4	53	9 M		36	18	2430	1170	416	2.4	18
Min	2	19			16	0	140	45	130	1.2	2.83
Mean		**32.00**			**20.89**	**7.78**	**375.67**	**226.28**	**168.28**	**1.27**	**5.55**
Std dev		9.32			5.88	4.95	531.42	268.29	89.01	0.28	3.82

Query 3 filtered on *patients* with at least possible DILI (Causality Score ≤ 4). Median age of 58 (blue oval) significantly higher than for volunteers (Tables 2 vs 1). Two cholestatic patients (R-values < 2.0) highlighted. (red ovals)

Table 2. Query 3 tabular data from DILI consult IND-1—Patient

ID	Causality Score	Age (yr)	Gender	Hy's Law	Latency from start drug (da.)	Latency from stop drug (da.)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak
32010203	3	58	F	FALSE	16	-1	63	144	507	1.0	0.36
32310303-2	4	46	M	FALSE	11	-10	477	194	338	3.2	4.18
32320107	3	84	M	FALSE	41	0	288	124	2842	21.1	0.29
Median		**58**			**16**	**-1**	**288**	**144**	**507**	**3.2**	**0.36**
Max	4	84			41	0	477	194	2842	21.1	4.08
Min	3	46			11	-10	63	124	338	1.0	0.29
Mean		**62.7**			**22.7**	**-3.7**	**276.0**	**154.0**	**1229.0**	**8.4**	**1.6**
Std Dev		15.9			13.1	4.5	169.2	29.4	1142.6	9.0	1.8

Three cases of potentially chronic DILI (red bold) identified by the long negative latencies meaning patients were still on drug and washout to normal ALT took more than 6 months to resolve in 2 and did not resolve (listed as "NA) in the third. (Table 3) Median latency from drug start was comparatively short and tightly clustered around a mean of 44.6 days (green bold)

Table 3. Modified Query 3 tabular data from DILI Consult IND 2.

ID	Causality Score	Age	Gender	Race	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)	ALT peak	AST peak	ALP peak	Bilirubin peak	Washout ALT normal (da)
10-05035	3	77	F	White	**TRUE**	46	1	2364	1554	435	3.1	NA
10-45011	3	62	F	White	**TRUE**	36	0	3535	1669	262	7.77	47
10-03004	4	77	F	White	FALSE	45	-3	217	211	NA	1.2	NA
10-05005	**4**	**69**	**F**	**White**	**FALSE**	**83**	**-78**	**324**	**339**	**NA**	**1.2**	**NA**
10-18003	4	77	F	White	FALSE	48	-1	235	183	NA	1.2	33
10-18005	4	56	F	White	FALSE	44	-28	296	355	NA	1.2	99
10-34002	4	74	M	White	FALSE	38	-4	477	399	NA	1.2	37
10-40001	4	76	F	White	FALSE	35	-7	488	226	NA	1.2	33
10-43013	4	64	M	White	FALSE	41	-24	137	129	NA	1.2	16
10-45007	**2**	**68**	**F**	**White**	**FALSE**	**42**	**-311**	**361**	**258**	**NA**	**1.2**	**357**
10-58007	4	75	M	White	FALSE	46	-3	446	193	NA	1.2	50
60-04003	**3**	**69**	**F**	**White**	**FALSE**	**45**	**-81**	**318**	**181**	**NA**	**1.2**	**182**
60-06003	4	57	F	White	FALSE	41	-2	421	232	130	1.2	37
70-02005	4	75	M	White	FALSE	42	0	430	192	NA	1.2	23
80-02007	4	60	M	White	FALSE	36	-2	669	246	NA	1.2	22
90-03002	4	69	F	White	FALSE	45	-2	420	193	NA	1.2	41
Median		***69***				***43***	***-3***	***421***	***229***	***NA***	***1.2***	***37***
Min		***56***				***35***	***-311***	***137***	***129***		***1.2***	***16***
Max		***77***				***83***	***1***	***3535***	***1669***		***7.8***	***357***
Mean		***69.1***				***44.6***	***-34.1***	***696.1***	***410.0***		***1.7***	***75.2***
Std Dev		***7.1***				***10.6***	***75.9***	***884.8***	***459.7***		***1.6***	***91.8***

Summary

- Data entry by the ORISE Fellow was approximately 95% accurate.
- Medical officer estimated that PLADD saved about 2 work hours/IND
- Use of PLADD helped identify an age difference between DILI in healthy volunteers and patients, and a cholestatic injury in patients overlooked in previous DILI consultations for this IND.
- Use of PLADD drew attention to a potential chronic DILI that might have otherwise gone unnoticed without PLADD's Queries.
- PLADD highlighted a short and narrowly distributed latency from drug start that helped justify a partial, rather than full, clinical hold.

Conclusions

- Data entry into PLADD can be done accurately by non-medical officers without prior expertise in DILI.
- Medical officers still need to verify manual data entry and assess cases.
- PLADD can increase efficiency in DILI assessment by creating a structured, searchable database of assessments.
- PLADD can help identify drug specific DILI signatures (e.g., typical latencies and patterns of injury) as well as important outliers that might otherwise be overlooked.
- Because PLADD is Access® based, it is amenable to computer upload of data from ADaM or STDM datasets in NDAs and BLAs obviating the need for manual entry.