PROCEDURAL APPROACH TO MITIGATING CONCURRENTLY APPLIED CLINICAL PRACTICE GUIDELINES

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Clinical Practice Guideline (CPG)

- Clinical algorithm
  - Evidence-based best practice in healthcare
  - Guides diagnosis, management and treatment of a single condition
  - Might be represented in multiple different (and not always compatible) formats
- A valid therapy always exists for a single CPG
Clinical Practice Guideline (CPG)

Diagnosis and Management of Placenta Previa

This guideline has been reviewed by the Clinical Obstetrics Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

**Abstract**

Objectives: To review the use of transvaginal ultrasound for the diagnosis of placenta previa and recommend management based on accurate placental localization.

Options: Transvaginal sonography (TVS) versus transabdominal sonography for the diagnosis of placenta previa: route of delivery, based on placental edge to internal cervical os distance.

1. Sonographers are encouraged to report the actual distance from the placental edge to the internal cervical os at TVS, using standard terminology of millimeters away from the os or millimeters of overlap. A placental edge exactly reaching the internal os is described as 0 mm. If the placental edge reaches or overlaps the internal os on TVS between 19 and 24 weeks' gestation, a follow-up examination for placental location in the third trimester is recommended. Overlap of more than 15 mm is associated with an increased likelihood of placenta previa at term. (I-2A)

2. When the placental edge lies between 20 mm and 40 mm from the internal os, ultrasound should be repeated at regular intervals depending on the gestational age, distance from the internal os, and clinical features such as bleeding, because continued changes in placental location is likely. Overlap of 20 mm or more at any time in the third trimester is highly predictive of the need for Caesarean section (CS). (I-2B)

3. The os-placental edge distance on TVS after 19 weeks' gestation is informative in planing route of delivery. When the placental edge lies > 20 mm away from the internal cervical os, women can be offered a trial of labour with a high expectation of success. A distance of 20 to 0 mm from the os is associated with a higher CS rate, although vaginal delivery is still possible depending on the clinical circumstances. (I-2A)

4. In general, any degree of overlap (0-11 mm) after 19 weeks is an indication for Caesarean section as the route of delivery. (I-2A)

5. Outpatient management of placenta previa may be appropriate for stable women with home support, close proximity to a hospital, and readily available transportation and telephone communication. (I-2C)

6. There is insufficient evidence to recommend the practice of cervical cerclage to reduce bleeding in placenta previa. (I-D)

7. Regional anesthesia may be employed for CS in the presence of placenta previa. (I-2B)

8. Women with a placenta previa and a prior CS are at high risk for placenta accreta. If there is imaging evidence of pathological adherence of the placenta, delivery should be planned in an appropriate setting with adequate resources. (I-2B)

**Validation:** Comparison with Placenta previa and placenta previa accreta: diagnosis and management. Royal College of Obstetricians and Gynaecologists. Guideline No. 27. October 2009.

The level of evidence and quality of recommendations are described using the criteria and classifications of the Canadian Task Force on Preventive Health Care (Table).
Gaps in CPG Research

• 50% of people 65 years old or older have a comorbid condition [Institute of Medicine, 2001]

    However…

• Most attention has been paid to an individual CPG instead of adapting the guidelines to manage comorbid condition
  • Creating formal/executable CPG representations (e.g., GLIF3, SAGE, Asbru or PROforma)
  • Translating unstructured text into formal CPG models (e.g., GEM Cutter, ERGO project)
  • Verifying CPG models (e.g. UML-based model checking, theorem proving using KIV prover, knowledge-based checking)
  • Using CPG models to assist MD take actions (Model checking using temporal logics, ASTI)
Combining CPGs

- Research on combining CPGs is still in its infancy and development of combined CPG is mostly expert-based
- Recent developments
  - GLINDA (GuideLine INteraction Detection Architecture)
    - Integration of ATHENA CDS in an agent-oriented architecture
    - Modeling tasks and methods in Protégé
  - COMET
    - Ontology mapping-based approach [Abidi and Abidi, 2009]
  - CPG templates and composition operators [Riano and Collado, 2013]
- Our research combines:
  - Graph Theory
    - CPG translation, Loop detection
  - Constraint Logic Programming
    - CPG representation, Therapy construction
Problem Statement

How to create an executable model of complex guidelines that can be applied to a patient with comorbidity?

Rationale

• Pressing need in clinical practice to mitigate adverse interactions for multiple concurrently applied disease-specific clinical practice guidelines
• CPGs include challenging characteristics
  • Numerical measurements such as medication dosages
  • Iterative actions forming a cycle
• Our goal: Automate the mitigation process and provide decision tool to support a physician at the point of care
Clinical Case Study

- Concurrent application of CPGs for a patient who is being treated for Wolff Parkinson White Syndrome (WPW) and suffers an Atrial Fibrillation (AF)
  - Common comorbid condition managed in the ED
  - Overlapping and possibly contradicting treatments
  - Dosages of medication need to be adjusted depending on other measurements
  - Repeated actions that manifest themselves as loops in the CPG
    - Number of iterations is not explicit
Mitigation Approach Overview

- Two CPGs applied to patient with comorbid conditions to obtain combined consistent therapy
- Combined therapy does not exist in case of adverse interactions between individual therapies
  - Direct adverse interactions caused by contradictory actions (e.g., to give medication A, not to give medication A)
  - Indirect adverse interactions caused by drug-drug or drug-disease interactions (e.g., giving medication A is forbidden when some disease is present)
- Mitigation (identification and addressing) of adverse interactions requires clinical acumen (experts, textbooks, clinical evidence)
- Clinical acumen encoded in form of operators
  - Interaction operators to model indirect adverse interactions
  - Revision operators to model revisions
Key Concepts: Actionable Graphs and Paths

- Actionable graph \((AG_i)\) for \(CPG_i\) is defined as a directed graph
  \[ AG_i = \langle N_i, A_i \rangle \]

- \(N_i\) = set of context, action and decision nodes
  - Context node provides clinical context, \(AG_i\) has a context node as its root, indicating the disease handled by \(CPG_i\).
  - Action node corresponds to an action step from \(CPG_i\)
  - Decision node corresponds to a decision step from \(CPG_i\)

- \(A_i\) = set of arcs representing transitions between nodes

- Inspired by SDA* (State-Decision-Action) formalism for CPGs [Isern et al., 2009], created from various representations [Hing et al., 2010]
Key Concepts: Actionable Graphs and Paths

**Actionable graph for WPW**

- Patient diagnosed with WPW
- Initial dosage of F (DF₀=DF_{low})
- WPW stable (W_{Sk})
  - Yes: Keep dosage of F (DF=DF_{k})
  - No: Adjust dosage of F (DF(k+1)=DF_{k}+\Delta DF) < DF_{safe}(P)
- Current dosage of F (DF_{k}) ≥ DF_{safe}(P)
- Another therapy (AT)
- Discharge patient (DP)

**Actionable graph for AF**

- Patient diagnosed with AF
- Hemodynamic instability (HI)
  - Yes: Structured heart disease (HD)
  - No: Electrical cardioversion (EC) Amiodarone IV (AIV) Flecainide IV (FIV)
- Recurring AF episode (RAE)
  - Yes: Oral amiodarone (A)
  - No: Discharge patient (DP)

All paths enumerated from root to leaves
Supporting Complex CPGs

- Numerical measurements (e.g. medication dosages)
  - Requires non-binary decisions and actions
  - **Approach:** use numeric variables
    - Action variables support finer grained details
      - \((Flecainide := True / False)\) versus \((Flecainide := [0…500])\)
    - Decision variables are not discretized
      - if \(Flecainide > 150 \land Flecainide < 300\)

- Repeated actions (e.g. re-testing or monitoring)
  - A node in an AG can be traversed one or more times
  - **Approach:** allow for algorithmic expressions and conditions by flattening loops
    - \(\neg(A \land DF = DF_{max}) \land (DF = DF_1 + DF_2 + DF_3 + …)\)
Supporting Repeated Actions

• Find and expand loops in AGs

procedure expand(in AG\textsubscript{i}, in WorstCase\textsubscript{i}, out AG\textsubscript{i}\textsubscript{exp})
begin
1. Loop\textsubscript{i} := identify_loop(AG\textsubscript{i})
2. MaxIter\textsubscript{i} := check_conditions(Loop\textsubscript{i}, WorstCase\textsubscript{i})
3. ForwardPath\textsubscript{i} := create_path(Loop\textsubscript{i}, MaxIter\textsubscript{i})
4. AG\textsubscript{i}\textsubscript{exp} := replace_loop(AG\textsubscript{i}, ForwardPath\textsubscript{i})
5. return AG\textsubscript{i}\textsubscript{exp}
end

• Loop\textsubscript{i} found using a path-based strong component algorithm (Tarjan’s)
  • Assumes a single loop in the AG
• WorstCase\textsubscript{i} is defined according to patient information and secondary knowledge (expert's opinion, evidence, literature, …)
• Flatten loop and replace it with ForwardPath\textsubscript{i}
Supporting Repeated Actions

Original AG\textsubscript{WPW}

- Patient diagnosed with WPW
  - Dosage of F (DF\textsubscript{0}=50mg/day)
    - WPW stable (WS\textsubscript{0})
      - DF\textsubscript{1}=DF\textsubscript{0}
    - Adjust dosage of F (DF=kDF\textsubscript{0}+k\Delta DF)
      - DF\textsubscript{1}=DF\textsubscript{0}+k\Delta DF
    - DF\textsubscript{1}<DF\textsubscript{max}
      - Another treatment (AT)
      - DF=DF\textsubscript{k}
      - Patient release (PR)

Revised AG\textsubscript{WPW}

- Patient diagnosed with WPW
  - Dosage of F (DF\textsubscript{0}=50mg/day)
    - WPW stable (WS\textsubscript{0})
      - DF\textsubscript{0}=DF\textsubscript{0}
    - Adjust dosage of F (DF\textsubscript{1}=DF\textsubscript{0}+\Delta DF)
      - DF\textsubscript{1}=DF\textsubscript{0}+\Delta DF
      - WPW stable (WS\textsubscript{1})
        - DF\textsubscript{1}=DF\textsubscript{1}
      - DF\textsubscript{1}<DF\textsubscript{max}
        - Adjust dosage of F (DF\textsubscript{2}=DF\textsubscript{0}+2\Delta DF)
          - DF\textsubscript{2}=DF\textsubscript{0}+2\Delta DF
          - WPW stable (WS\textsubscript{2})
            - DF\textsubscript{2}=DF\textsubscript{2}
            - DF\textsubscript{2}<DF\textsubscript{max}
              - Adjust dosage of F (DF\textsubscript{3}=DF\textsubscript{0}+3\Delta DF)
                - DF\textsubscript{3}=DF\textsubscript{0}+3\Delta DF
                - DF=DF\textsubscript{3}
                - Another treatment (AT)
                - DF=DF\textsubscript{3}
                - Patient release (PR)

- Another treatment (AT)

- Patient release (PR)
Key Concepts: Logical Models

• A logical model \((LM_i)\) provides a logical representation of an \(AG_i\)

\[
LM_i = <d_i, V_i, PLE_i>
\]

• \(d_i\) = label of disease associated with \(AG_i\)
• \(V_i\) = set of action and decision variables associated with actions and decision nodes in \(AG_i\)
• \(PLE_i\) is a set of logical expressions representing paths in \(AG_i\)
Key Concepts: Logical Models

Logical Model created from $AG_{AF}$

$$d_{AF} = AF$$
$$V_{AF} = \{HI, EC, HD, AIV, FIV, RAE, A, PR\}$$
$$PLE_{AF} = \{HI \land EC \land RAE \land A \land PR \land \neg FIV \land \neg AIV, \neg HI \land EC \land \neg RAE \land PR \land \neg FIV \land \neg AIV \land \neg A, \neg HI \land HD \land AIV \land RAE \land A \land PR \land \neg EC \land \neg AIV, \neg HI \land \neg HD \land AIV \land \neg RAE \land PR \land \neg EC \land \neg FIV \land \neg A, \neg HI \land \neg HD \land FIV \land RAE \land A \land PR \land \neg EC \land \neg AIV, \neg HI \land \neg HD \land FIV \land \neg RAE \land PR \land \neg EC \land \neg AIV \land \neg A\}$$

Example variables and domains
- HI (hemodynamic instability) = \{yes, no\}
- HD (structured heard disease) = \{yes, no\}
- RAE (recurring AF episode) = \{yes, no\}
Key Concepts: Combined Logical Models

- A combined logical model \((CLM_{i,j})\) brings together a pair of logical models and information about adverse interactions between underlying CPGs
  \[ CLM_{i,j} = <LM_i, LM_j, ILE_{i,j}> \]

- \(LM_i \& LM_j\) = individual logical models representing \(AG_i\) and \(AG_j\)

- \(ILE_{i,j}\) = logical expressions that represent indirect adverse interactions between \(CPG_i\) and \(CPG_j\)
  \[ ILE_{WPW, AF} = \{ \neg (A \land DF = DF_{max}) \} \]
What is a Consistent Therapy?

- Solution to combined logical model (CLM) == consistent therapy
  - Action variables returned to physician describe proposed therapy
  - Adverse interactions mitigated by applying revision operators to CLM
    - Adverse interactions and revisions (if any) returned
- ECL\textsuperscript{i}PS\textsuperscript{e} system used to represent and solve a CLM
  - Provides access to various solving techniques
  - \textit{Repair} library used to identify violated constraints via conflict sets
Discussion and Future Work

• **Contribution:** Logical-based approach to mitigate multiple CPGs
  - Executable represents of CPGs and secondary knowledge
  - Support complex relationships
  - Identify and expand repeated actions

• **Benefit:** Steps towards
  - A comprehensive alerting system for physicians at the point of care
  - Wider acceptance of CPGs in clinical practice [Sittig et al. 2008]

• **Future Work:** Develop a formal theory for mitigation
  - Formalizing all critical attributes (iterations, concurrency, time, interrupts and reactions, sub-components, uncertainty, and even trust) needed to fully describe primary and secondary knowledge
Thank you!